FOOD AND DRUG ADMINISTRATION
DIVISION OF ANTI-INFLAMMATORY, ANALGESIC AND OPHTHALMIC DRUG PRODUCTS -- HFD-550

Medical Officer Review

NDA 21-042 and NDA 21-052
(Rofecoxib tablets and rofecoxib oral solution)

Re: Complete response to Approvable letter for 21-042/S 007 and 21-052/S 004

Submission date (letter):	July 12, 2001
End of Review date:	November 28, 2001
Reviewer:	Maria Lourdes Villalba, M.D.
Applicant:	Merck Research Laboratories
Pharmacologic category:	NSAID (COX-2 inhibitor)
Proposed indications:	Management of acute pain, dysmenorrhea and signs and symptoms of osteoarthritis.
Dosage form and route:	Oral capsule, 12.5, 25 mg and 50 mg Oral solution 12.5 mg/5ml and 25 mg/5ml
Project Manager:	
Related reviews:	NDA 21-042/S007 (VIGOR study)
Consults:	Douglas Throckmorton, M.D. (HFD-110) Eric Bastings, M.D. (HFD- 120)

Orig NDA # 21042s007
HFD-550/Div File
HFD-550/PM/Gould
HFD-550/Statistics/SLin/QLi
HFD-550/MO/Villalba
HFD-550/TL/Goldkind
HFD-110/DDD/Thorckmorton
HFD-120/MO/EBastings

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Clinical Review
NDA 21-042/s007
Complete Response to Approvable Letter (4/7/01)

Executive Summary

I. Recommendations

A. Recommendation of Approvability

NDA 21-042/s007 should be Approved including labeling language that reflects available overall safety, gastrointestinal safety and cardiovascular safety in the VIOXX databases. Until prospective, randomized, adequately powered studies are performed, rofecoxib should be used with caution in patients with known cardiovascular risk, congestive heart failure and hypertension. FDA proposed labeling was sent to the applicant in October 15, 2001.

B. Recommendation on Phase 4 studies and/or Risk Management Steps

If the sponsor proposes a new indication such as a preventive claim, studies should not exclude patients at high cardiovascular risk, should be adequately powered to detect statistical significant differences in cardiovascular safety and should incorporate overall safety, including total cause mortality, as part of the safety endpoints.

The sponsor should consider long term safety studies of rofecoxib in patients taking low dose aspirin to assess cardiovascular, gastrointestinal and overall safety in this population.

II. Summary of Clinical Findings

A. Brief Overview of the Submission

The Complete Response to the Approvable letter issued to NDA 21-042/s007 in April 7, 2001 includes the report of the **ADVANTAGE** study (a 3-month study of rofecoxib 25 mg/day and naproxen 500 mg twice daily in approximately 5600 patients with osteoarthritis -OA-) and a **Safety Update Report (SUR)** (long-term follow up of patients in the original OA program and safety data from studies not previously submitted to the FDA). For completeness, a summary of the preliminary

safety review of the rheumatoid arthritis (RA) efficacy application (NDA 21-042/s012) is included in this document. The RA efficacy supplement evaluated rofecoxib 25 and 50 mg doses. The active comparator was naproxen 500 mg twice daily. The current review focuses on overall safety and cardiovascular safety from all these databases.

B. Efficacy – Not applicable

C. Safety

1. The following findings apply to the ADVANTAGE and RA safety databases:

   a. Rofecoxib (25 or 50 mg) showed no overall safety advantage over naproxen 500 mg twice daily as measured by total number of deaths, serious AE's, hospitalizations, discontinuations due to AE's, and common AE's.

   b. Rofecoxib (25 or 50 mg) was associated with a nominally higher incidence of discontinuations due to HTN, edema and CHF-related events compared to naproxen 500 mg twice daily.

   c. Rofecoxib (25 mg or 50 mg) was associated with a nominally higher cardiovascular thrombotic risk (particularly an increased risk of MI) as compared to naproxen 500 mg twice daily.

   These trends (a, b and c) were observed in all studies that compared rofecoxib to naproxen: in OA and RA patients; users and non-users of low dose ASA for cardiovascular prophylaxis; short term studies (3 months) and long-term follow up datasets (up to 3 years). These findings are highly consistent with those in VIGOR, a large prospective outcome study that compared rofecoxib 50 mg daily to naproxen 500 mg twice daily over a median treatment period of 9 months. In VIGOR rofecoxib was associated with two fold risk of developing cardiovascular thrombotic events (p=0.001) and higher incidence of dropouts due to hypertension, edema and CHF related events compared with naproxen.

   The reason for the increased cardiovascular risk with rofecoxib 25mg and 50 mg compared to naproxen is still unknown.

2. Cardiovascular safety of rofecoxib compared to NSAIDs other than naproxen.

   There is a spectrum of COX-1/COX-2 selectivity among NSAIDs. There are no adequate long-term data comparing the cardiovascular risk of rofecoxib to traditional NSAIDs other than naproxen. Studies in the original NDA 21-042

and the SUR, were inadequate in size and duration to assess safety differences (particularly GI and CV) between either dose of rofecoxib and individual NSAIDs. Meta-analyses of small studies of different design and duration using different NSAIDs and different doses of rofecoxib are not adequate to assess whether rofecoxib has a cardiovascular safety profile similar to other NSAIDs.

3. Cardiovascular safety of rofecoxib compared to placebo.

   Data from the original NDA 21-042 and the SUR (including one-year placebo-controlled data from three studies of rofecoxib 25 mg in the prevention of Alzheimer's disease) do not provide adequate evidence that rofecoxib has a cardiovascular safety profile similar to placebo. Total cause mortality in the Alzheimer's studies was higher in rofecoxib (n=33) compared to placebo (n=20) (p=0.07, crude rate comparison). Of those, 9 and 4 were confirmed cardiovascular thrombotic deaths in the rofecoxib and placebo group respectively. Of note, although this was an elderly population (mean age 75 years), patients at high cardiovascular risk were not enrolled.

D. Dosing

Large studies included in this application used the 25 mg dose. Cardiovascular thrombotic events, hypertension, edema and congestive heart failure-related findings at the 25 mg dose were consistent in trend with the rofecoxib 50 mg dose.

E. Special Populations

1. Gender, age, race.

Effects of gender, age and race have not been addressed in this supplement. For the purpose of addressing CV or GI safety, the number of cases is small.

2. Population using low dose aspirin for cardiovascular prophylaxis.

There are no adequate long term data on concomitant use of rofecoxib in patients taking low dose aspirin (ASA) for cardiovascular prophylaxis. Limited available data from ADVANTAGE suggest that:

- the use of low dose ASA for cardiovascular prophylaxis may not eliminate the excess of cardiovascular events on rofecoxib 25 mg compared to naproxen among those patients at known cardiovascular risk.

- the use of prophylactic low dose ASA may eliminate the GI advantage of rofecoxib compared to naproxen.

Clinical Review

I. Introduction and Background

Rofecoxib (VIOXX) is a non-steroidal anti-inflammatory drug (NSAID) with selective COX-2 inhibitory properties. VIOXX was approved in May 1999 for the signs and symptoms of osteoarthritis (OA) at the doses of 12.5 and 25 mg once a day, and for the management of acute pain in adults and dysmenorrhea (50 mg once a day). The use of VIOXX in children younger than 16 years of age has not been studied.

There are currently multiple NSAID products approved for the above indications. Celecoxib (CELEBREX), another COX-2 selective NSAID, is approved for OA, rheumatoid arthritis (RA) pain and for the prevention of polyps in patients with familial polyposis.

NDA 21-042/s007 was submitted in June 29, 2000. The submission included the "VIGOR" study (VIOXX Gastrointestinal Outcome Research study), studies 085 and 090 and preliminary safety data from a large study referred to as the "ADVANTAGE" study (For a detailed review of this submission the reader is referred to the 3/30/01 medical officer review). NDA 21-042/s007 proposed the removal of the NSAID template GI WARNING section of the VIOXX label. Review of the data supported some modification but not removal of the GI WARNING section of the VIOXX label. Additionally, rofecoxib 50 mg showed no advantage in overall safety compared to naproxen 500 mg twice daily (deaths, serious adverse events, discontinuations due to adverse events) and raised new concerns regarding the cardiovascular safety of VIOXX: increased risk of serious cardiovascular thrombotic events with rofecoxib compared to naproxen (RR 2.37, p =0.0016).

In April 6, 2001, FDA issued an Approvable letter to supplement 007 noting that changes from VIGOR should be incorporated into the label. However, to optimally characterize the safety profile of VIOXX - particularly overall safety and cardiovascular safety – at doses indicated for chronic use in a patient population that did not specifically exclude low dose aspirin use, the division requested that the complete report of the ADVANTAGE study be submitted for review.

II. Description of Clinical Datasources

The current document includes the review of:

- The complete report of the **ADVANTAGE** study (submitted in pieces 3/30/01, 4/13/01 and 4/16/01).

- The **Safety Update report (SUR)**(submitted 7/12/01) which includes serious adverse events from the extension studies submitted in the original OA program (studies 029, 058, 034 and 035) and from studies that had not been previously submitted to the FDA: studies 083 (bone mineral density); 120 and 121 (low back

pain); 118 (prostatitis pain); 903 (OA); five small studies of ≤ 6weeks duration comparing rofecoxib to other NSAIDs and studies 078, 126 and 091 (prevention of Alzheimer's).

- Safety data from the **RA efficacy application** database (NDA 21-042/s012, submitted 2/28/01). (A summary of the Safety review is included in this document. A more detailed safety review and the Efficacy of the RA supplement are presented in a separate review).

- Additional data submitted in response to specific FDA requests for information (7/26, 7/30, 8/04, 8/17, 9/20, 20/01, 10/03, 10/05, 10/08, 11/05, 11/26/01).

III. Clinical Review Methods

The review was conducted by corroboration of sponsor's tables against full listings of adverse events as well as reviewing case report tabulations, selected case report forms and adjudication packages for cardiovascular events. Consults were obtained from the Division of Cardio-Renal (HFD-110) and Neuropharm (HFD-120) products for evaluation of specific cases where HFD-550 reviewer had concerns over accuracy of case adjudication. Published literature related to preclinical and clinical studies of COX-2 inhibitors was reviewed.

The trials appeared to be conducted in accordance with accepted ethical standards.

Evaluation of Financial Disclosure is not applicable. The main study in this application – the ADVANTAGE study – was not a covered study.

IV. Integrated Review of Efficacy – Not applicable

ADVANTAGE was a safety study. The SUR contained no efficacy data. The efficacy of the RA supplement (s012) is reviewed separately.

V. Integrated Review of Safety

A. Brief Statement of Conclusions:

1. ADVANTAGE

ADVANTAGE was a double blind, randomized, 12-week controlled study (mean duration of exposure 69 ± 30 days), comparing rofecoxib 25 mg/day to naproxen 1000 mg/day in patients with osteoarthritis. Approximately 2700 patients were randomized into each treatment arm. Approximately 13% of patients were taking low dose aspirin for cardiovascular prophylaxis in each treatment group.

a. Rofecoxib 25 mg – the dose approved for chronic use - showed no overall safety advantage over naproxen 500 mg twice daily, as measured by the total number of deaths, serious adverse events (AE's), discontinuations due to

clinical/ laboratory AE's compared to naproxen. This is somewhat striking, given the theoretical assumptions of the COX-2 hypothesis and literature publications suggesting that COX-2 selectivity would provide superior safety than non-selective NSAIDs.

Table 1. ADVANTAGE Overall Safety parameters. Percentage of patients with events.

	Rofecoxib 25 mg (N= 2785)	Naproxen 500mg bid (N=2772)
Deaths	0.2	0.1
Serious AE	2.4	2.6
Dropouts AE	13.4	13.9
Hospitalizations	1.9	1.7
Dropouts Lab AE	0.4	0.2

b. Consistent with VIGOR, there was a trend of excess in serious cardiac thrombotic events in the rofecoxib 25 mg group, compared to the naproxen group (ten and three events, respectively, as per FDA review). There were five myocardial infarction (MI), two anginal events and three sudden deaths in the rofecoxib 25 mg group and one MI and two angina (no sudden deaths) in the naproxen group. There were also two and five ischemic cerebrovascular events in the rofecoxib and naproxen groups, respectively. Two of the four CVA's on naproxen were on concomitant estrogen replacement therapy. There were no hemorrhagic strokes in the naproxen group.

c. Consistent with VIGOR twice the number of patients discontinued due to cardiovascular related adverse events (40 and 21 from the rofecoxib and naproxen groups, respectively). More patients discontinued due to HTN related events (15 and 7); edema related events (19 and 12) and laboratory adverse events (11 and 6) in the rofecoxib 25 mg group as compared to the naproxen group. There were more CHF related events (11 and 6) in the rofecoxib group as compared to the naproxen group.

d. More patients discontinued due to serious GI events in the naproxen group (142) as compared to the rofecoxib 25 mg group (113). There were 1 and 4 confirmed complicated PUBs in the rofecoxib and naproxen arm, respectively. The number of clinically relevant GI events is small but the trend was consistent with the VIGOR study.

e. Special populations: co-use of low dose ASA for cardiovascular prophylaxis

- **Data suggest that the use of prophylactic ASA may not eliminate the excess of cardiovascular events on rofecoxib compared to naproxen.**

The number of investigator reported serious cardiovascular adverse events for all patients (ASA users and non-users) was 23 (0.8 %) and 17 (0.6%) in the

rofecoxib and naproxen groups, respectively. The number of these events in the subgroup of patients at known cardiovascular risk – as defined by concomitant use of low dose ASA – was 7/ 352 (2.0 %) and 2/ 367 (0.5 %) in the rofecoxib and naproxen group, respectively. These findings are not inconsistent with VIGOR, in which a post-hoc analysis conducted by the sponsor showed that the relative risk of developing serious cardiovascular thrombotic events for rofecoxib compared to naproxen increased from two fold in the whole population (RR:2.37, p= 0.001 for rofecoxib vs. naproxen) to five fold among those patients who might have benefited from prophylactic ASA (RR: 4.89, p= 0.01 for rofecoxib vs. naproxen).

If the cardiovascular findings in VIGOR were all explained by naproxen anti-platelet effect, a difference would not be expected between naproxen and rofecoxib in ADVANTAGE, when patients at risk in both treatment groups were already maximally protected by ASA.

- **Data suggest that the use low dose aspirin – such as the dose used for cardiovascular prophylaxis - may eliminate the GI advantage of rofecoxib over naproxen.**

The number of serious gastrointestinal adverse events for all patients in the trial showed a trend in favor of rofecoxib (n=7, 0.3%) as compared to naproxen (n= 21, 0.8%). In this short trial, co-use of low dose ASA increased the risk of serious GI events for rofecoxib (n=2 out of 352, 0.6%) but did not appear to increase the risk for naproxen (2 out of 367, 0.8%, unchanged). The ADVANTAGE study was too short and the number of events too small to adequately assess clinically significant GI events, particularly in the subgroup of patients using ASA, but the limited data suggest that the effects of low dose aspirin may counterbalance the COX-1 spearing effect of rofecoxib in the GI tract.

f. The findings of the ADVANTAGE study are consistent with those of the VIGOR and the RA efficacy databases. The CV findings are of concern because this is only a 12-week study, the dose of rofecoxib used in this study is 25 mg/day (half of the dose used in VIGOR), this was a different population of patients (OA instead of RA) and patients were allowed to use aspirin if indicated for cardiovascular prophylaxis. However, ADVANTAGE was not designed to address serious gastrointestinal or cardiovascular adverse events. It was too short and the number of clinically relevant adverse events was relatively small.

2. **Safety Update Report.**

There is no adequate evidence that rofecoxib has a cardiovascular safety profile similar to placebo or other NSAIDs.

a. Studies that compared rofecoxib to non-naproxen NSAIDs in the original NDA database and subsequently, involved too few patients to adequately assess differences in cardiovascular safety between rofecoxib and each NSAID. Studies with nabumetone were of 6 weeks duration; studies with ibuprofen were of 6 weeks to 6 months duration.; studies with diclofenac were of one year duration. Some of these studies had blinded extensions, but the actual number of patients exposed for a year or longer is very limited.

Meta-analyses of small studies of different duration, different size and different design, involving different patient populations and different doses of rofecoxib can not adequately assess the cardiovascular safety of rofecoxib compared to individual NSAIDs.

b. Analyses of data from the Alzheimer's studies provide valuable one- year placebo-controlled data in patients age 50 years or older. However, the studies were not powered to detect differences in cardiovascular safety between rofecoxib and placebo (approximately 1500 patients randomized per treatment arm, considering the three studies together). Additionally, the studies excluded patients who had an indication for aspirin prophylaxis and those taking estrogen replacement therapy. After enrollment was complete, a protocol amendment allowed the use of low dose aspirin in those patients who might benefit from it for cardiovascular prophylaxis. A small percentage of patients were put on low dose ASA (approximately 7%).

Although not a pre-specified endpoint, total cause mortality in the Alzheimer's studies was higher in the rofecoxib group (n=33) compared to the placebo group (n=20) (p= 0.07 for crude rate comparison). The trend of more deaths in the rofecoxib group as compared to placebo was consistent in study 091 and 078. Study 126 was terminated early due to lack of efficacy in study 091.

Of all deaths, eight and four were confirmed cardiovascular thrombotic deaths by the CV adjudication committee in the rofecoxib 25 mg and placebo groups, respectively. This finding suggests a drug effect, rather than a lack of anti-platelet effect of rofecoxib. There were no differences in the number of serious cardiovascular potentially thrombotic events referred for adjudication in each treatment group (approximately 60 in each). A detailed review of these cases is being conducted by the Division of Cardio-renal products (HFD-110).

3. RA efficacy supplement safety database

a. Consistent with VIGOR and ADVANTAGE, rofecoxib 25 and 50 mg showed no overall safety advantage over naproxen, as measured by the total number

of deaths, serious adverse events (AE's), discontinuations due to clinical and laboratory AE's and common AE's compared to naproxen.

b. Consistent with VIGOR and ADVANTAGE, rofecoxib 25 and 50 mg was associated with higher incidence of HTN, edema and CHF-related events compared to naproxen 500 mg twice daily. Incidence of HTN was consistently two to three fold higher for rofecoxib 25 and 50 mg as compared to naproxen.

c. Consistent with VIGOR and ADVANTAGE, the RA databases suggest an increased cardiovascular thrombotic risk (particularly an increased risk of MI) for rofecoxib 25 and 50 mg as compared to naproxen 500 mg twice daily. There were 4 MI in the rofecoxib 25 mg group (501 patient/years at risk), 5 MI and one sudden death in the rofecoxib 50 mg group (430 patient years at risk) and one MI in the naproxen group (406 patient years at risk).

B. Description of Patient Exposure

The ADVANTAGE study included approximately 5600 patients exposed to either rofecoxib 25 mg or naproxen 500 mg bid, with a median duration of exposure of 84 days.

The Safety Update Report includes approximately 4000 patients who received rofecoxib 25 or 50 mg of whom 1000 participated in extension studies to the original NDA OA program and 3000 participated in new studies not previously submitted to the Agency. The duration of these studies were from 4 weeks to 15 months. The size of the studies varied from a 50-patient per arm study to a 700-patient per arm study. The comparators were naproxen (approximately 500 patients), diclofenac/ misoprostol (approximately 500 patients) and ibuprofen (approximately 150 patients). The Alzheimer's studies randomized approximately 3000 patients to rofecoxib 25 mg (1500) or placebo (1500) and provide safety information for approximately 1500 patient years at risk. At the time of the submission (cut-off date for the SUR was April 2001) one of the three studies was completed (#091) one was ongoing (#078) and one had been terminated earlier (#126).

Approximately 1500 patients were randomized to rofecoxib 25 mg (n= 797) and 50 mg (n= 677) in 3-month placebo controlled studies. Approximately 180, 140 and 80 patients were exposed to rofecoxib 25mg, rofecoxib 50mg and naproxen 1000 mg respectively, for one year or more.

C. Summary of Critical Safety Findings and Limitations of Data

Consistent with the VIGOR study, a 8000-patient study of rofecoxib 50 mg and naproxen 1000 mg in patients with RA, the data reviewed in this submission (ADVANTAGE, SUR, RA efficacy) suggest an increased cardiovascular risk (cardiovascular thrombotic events, hypertension, edema, congestive heart failure) in

patients treated with rofecoxib 25 and 50 mg as compared with naproxen 1000 mg daily. The major limitations of these databases are

1. Patients at high cardiovascular risk regardless of the use of aspirin were excluded from most of the studies.

2. The majority of studies of rofecoxib did not allow inclusion of patients using prophylactic low dose ASA. The only large study that allowed prophylactic ASA was ADVANTAGE, a study too short to assess long term effects of co-use of rofecoxib and low dose ASA. (13% of patients were on low dose ASA in each group). A few other studies that allowed inclusion of patients on low dose ASA were small and shorter than 6 weeks.

3. Naproxen was the NSAID comparator for most trials (ADVANTAGE, VIGOR, RA efficacy studies). Comparative safety data to NSAIDs other than naproxen are limited to small numbers in relatively short trials.

4. The complete comparative safety information between rofecoxib and placebo in the Alzheimer's studies has not been provided. Listings of serious adverse events and deaths and adjudication packages for cases that were referred to the CV adjudication committee have been provided for all three studies. Discontinuations due to AE were provided only study 091. Full safety reports are to be submitted.

VI. Dosing, Regimen and Administration issues

VIOXX (rofecoxib) is approved for the treatment of the signs and symptoms of OA at the doses of 12.5 and 25 mg daily and for the management of acute pain in adults and dysmenorrhea, at the dose of 50 mg once a day.

Large studies included in this application used the 25 mg dose. Hypertension, edema and congestive heart failure related findings with rofecoxib 25 mg dose were consistent in trend with the 50 mg dose.
The current label states that the use of the 50 mg dose in acute pain for more than 5 days has not been studied. However, in view of the safety issues associated with the chronic use of 50 mg (i.e. hypertension, edema, congestive heart failure and cardiovascular thrombotic events) in the VIGOR study, the label should state that the chronic use of VIOXX 50 mg dose is not recommended.

VII. Use in Special Populations

A. Effects of gender, age and race have not been addressed in this supplement. Number of events are small to adequately assess CV or GI safety in these subgroups.

B. Comments on Data Available or Needed in Other Populations: Population using low dose aspirin for cardiovascular prophylaxis.

Available data from VIGOR and the RA efficacy database suggest an increased risk of serious cardiac thrombotic events in patients with prior cardiovascular risk taking rofecoxib 25 and 50 mg as compared to naproxen 500 mg twice daily. The sponsor has speculated that the excess risk in the rofecoxib group may be due to the lack of anti-platelet effect of rofecoxib compared to naproxen and that addition of low dose ASA in high risk patients may bring down that excess cardiovascular risk.

The limited data from the ADVANTAGE study suggest that the use of low dose ASA in patients with prior cardiovascular history, might not eliminate the excess risk of serious cardiovascular events of rofecoxib compared to naproxen. Patients on low dose aspirin prophylaxis showed a trend towards more cardiovascular events than those not requiring aspirin in the rofecoxib arm (2.0% and 0.5%). This was not the case in the naproxen treated subjects (0.6% and 0.5%, respectively). This information suggests that the excess risk of CV thrombotic events on rofecoxib as compared to naproxen may be due to some mechanism other than the antiplatelet effect of naproxen. (See IV, 1, d.).

The long term effects of rofecoxib on the cardiovascular and gastrointestinal system in patients taking low dose aspirin has not been adequately assessed.

VIII. Appendices

A. Review of Individual Studies

1.0 ADVANTAGE study

1.1 Protocol design

The ADVANTAGE study (**A**ssessment of **D**ifferences between **V**IOXX™ **A**nd **N**aproxen **to** **A**scertain **G**astrointestinal Tolerability and **E**ffectiveness) was a randomized, double-blind, multicenter, active-controlled, 12-week study to evaluate rofecoxib 25 mg q.d. and naproxen 500 mg b.i.d. in patients with osteoarthritis (Protocols 102 and 903-0A). The use of low dose aspirin for cardiovascular prophylaxis was allowed in the study. Acetaminophen was allowed as a rescue medication in a PRN basis.

The study enrolled approximately 5,500 patients with OA of the knee, hip, hands, or spine, involving 581 investigators in the United States (protocol 102) and 19 investigators in Sweden (protocol 903-0A), from March 1999 to April 2000. Both protocols were identical as written and as implemented, except that the Swedish protocol did not enroll patients with OA of the hands. The data from both protocols were combined into one dataset, and the methods and results sections of this study report describe both protocols as a single study.

> *Reviewer's note: Although the title suggests that the protocol evaluated the effectiveness of rofecoxib, this was a safety study. The heterogeneity of the population regarding OA signal joint and the endpoints used in this trial do not allow adequate efficacy assessments. The trial was intended as a GI tolerability study. The primary hypothesis was GI tolerability but given size of the study, overall safety is as important as GI safety from the Public Health and consumer awareness point of view.*

1.2 Eligibility criteria

In general, the inclusion/exclusion criteria were similar to those used for other rofecoxib trials. The main differences between VIGOR and ADVANTAGE were:

1. **ADVANTAGE included a population of patients with OA instead of RA.**

2. **Patients taking low dose aspirin (ASA) for cardiovascular prophylaxis were allowed in the ADVANTAGE study. Patients with recent history of MI, TIA or stroke were not explicitly excluded from the study. However, similar to VIGOR, patients on warfarin, heparin, ticlopidine and high dose aspirin were not to be included in the study.**

Low dose ASA was defined for this study as doses of 81 mg/day or less. Some patients took up to 325 mg/day during the trial and they were included under the low-ASA user group.

1.3 Endpoints

The primary variable was GI tolerability, defined by the sponsor for this particular protocol as the cumulative incidence of discontinuation due to a GI AE (digestive events and abdominal pain). Other safety measures were AE incidence profiles, vital signs, and laboratory evaluations. Clinical data were collected during clinic visits (at baseline, at 6 and 12 weeks and early discontinuation) and via telephone contact (at 3 and 9 weeks of therapy). Laboratory parameters were measured at entry, week 12 and at early discontinuation visits.

Reviewer's comment: This review will focus on the overall safety, cardiovascular safety and NSAID-related AE's.

All subgroup safety analyses, including ASA user subgroups, were performed post hoc. All post hoc analyses were specified in the Data Analysis Plan (DAP), and most parameters were established prior to study unblinding, except the analysis of cardiovascular thrombotic events and the analysis of the number of perforations, ulcerations, and GI bleeds (PUBs) confirmed by adjudication and per 100 patient years.

1.4 Results.

1.4.1 Patient disposition and accounting is presented in Table 2.

Table 2. Patient disposition and accounting (Source: Sponsor's Table 20)

	Rofecoxib 25 mg qd	Naproxen 500mg bid
Patients randomized	2799	2787
Patients treated	2785	2772
Discontinued	757 (27.2)	788 (28.4)
Clinical AE	374 (13.4)	386 (13.9)
Laboratory AE	11 (0.4)	5 (0.2)
Protocol deviation	29 (1.0)	24 (0.9)
Lost to follow up	52 (1.9)	64 (2.3)
Withdrew consent	89 (3.2)	112 (4.0)
Lack of efficacy	177 (6.4)	176 (6.3)
Other	25 (0.9)	21 (0.8)

Similar number of patients discontinued from each treatment group (27-28%). The cause of discontinuation was also similar in both treatment groups. Of note, a relatively high number of patients (89 (3%) and 112 (4%) in the rofecoxib and naproxen arm, respectively) withdrew consent.

Reviewer's comment: Sponsor states that due to questionable validity, data from the 12 patients enrolled from site No. 378 were excluded from all analyses. These patients are not included in the total patient count noted above.

1.4.2 Demographic characteristics

The two treatment groups had similar demographic characteristics, arthritis treatment history at baseline and history of GI symptoms associated with NSAID use. The majority of patients were female (71.0%), and most were white (86.8%). The mean and median duration of disease were similar for both groups (approximately 69 and 84 months, respectively).

The majority of patients had used only NSAIDs prior to study entry (approximately 62% in each group). Approximately 15% had stopped NSAID treatment due to GI symptoms in the past in each arm. Patient age ranged from 36 to 97 years, with a mean age of 63 years. The most common signal joint was the knee followed by hand, spine and hip.

Reviewer's comment: The rofecoxib group included somewhat more patients with knee OA and less patients with hip OA as compared to the naproxen group. Since this is not an efficacy study, this difference is irrelevant.

1.4.3 Secondary diagnoses

The incidence of secondary diagnoses at entry were similar in both groups. Of note, 58.6% and 60.6% of patients had a diagnosis related to the cardiovascular system in the rofecoxib and naproxen groups, respectively. Approximately 45% of patients in each group had a history of hypertension.

Reviewer's comment: The percentage of patients with diagnoses related to the CV system is similar, but a 2 % difference represents 50 more patients with history of cardiovascular disease in the naproxen group and may meaningfully impact cardiovascular event rates..

1.4.4 Prior medications

The most common medications received within 30 days prior to visit 1 were acetaminophen (38%), celecoxib (19%), ibuprofen (19%) conjugated estrogenic hormones (17%) and aspirin (17%). Prior medications related to the cardiovascular system, coagulation system and hormonal replacement are presented in Tables 3, 4 & 5.

Table 3. ADVANTAGE: Prior medication related to the cardiovascular system

	Rofecoxib 25 mg/d N= 2785		Naproxen 1000 mg/d N= 2772	
	n	%	n	%
Renin-angiotensin system	593	(21.3)	614	(22.2)
Antihypertensives	132	(4.7)	149	(5.4)
Beta blocking	390	(14.0)	418	(15.1)
Calcium channel blockers	408	(14.6)	440	(15.9)
Cardiac therapy	114	(4.1)	127	(4.6)
Diuretics	536	(19.2)	560	(20.0)
Peripheral vasodilators	13	(0.5)	16	(0.6)
Serum lipid reducing agents	564	(20.3)	523	(18.9)

(source Sponsor's Table 14, appendix 1.4)

Table 4. Prior use of antithrombotic agents

	ROFECOXIB 25 MG N= 2785		NAPROXEN 1000 MG N= 2772	
	n	%	n	%
Clopidogrel bisulfate	4	(0.1)	7	(0.3)
Dipyridamole	4	(0.1)	10	(0.4)
Ticlopidine	1	(0.1)	0	
Warfarin sodium	6	(0.3)	1	(0.0)

(source Sponsor's Table 14, appendix 1.4)

Reviewer's comment: Similar percentage of patients had received cardiovascular medication and discontinued antithrombotic therapy within 30 days of entering the study. At the reviewer's request the sponsor provided information that none of these patients developed a serious cardiovascular thrombotic event during the trial.

Table 5. Advantage: Prior use of hormonal therapy

	Rofecoxib 25 mg/d N= 2785		Naproxen 1000 mg/d N= 2772	
	n	%	n	%
Endocrine therapy[1]	86	(3.1)	64	(2.3)
Sex hormones and modulators of the genital system[2]	875	(31.4)	859	(31.0)

Soruce: Sponsor's Table 14. Appendix 4.1) [1]: Endocrine therapy includes mainly raloxifene and tamoxifen. [2]: Sex hormones includes mainly estrogenic and progesterone-related hormones.

There were no significant differences in the number of patients who took hormone replacement therapy (HRT) prior to the trial. Approximately 31 % of patients took "hormones and modulators of the genital system" during the trial, including different estrogenic preparations with or without progesterone (n=741 and 720) progestins alone (n=145 and 151) or testosterone (n=12 and 10) in the rofecoxib and naproxen group respectively.

ASA was a prior medication in 470 (16.9%) and 474 (17.1%) patients in the rofecoxib and naproxen groups, respectively. Aspirin is listed among the analgesic, regardless of the dose that was taken.

> *Reviewer's comment. The sponsor did not specify the dose of ASA taken prior to entry. Of note, 360 and 372 patients used concomitant ASA during the study, in the rofecoxib and naproxen group, respectively. Therefore, approximately 100 patients in each arm discontinued the use of ASA before entering the study. At the reviewer's request the sponsor provided information that only one of the patients who discontinued ASA prior to study entry developed a serious CV thrombotic event (AN 2401) who was taking ASA 1300 mg/day for the treatment of OA, not for cardioprotection. This patient (on rofecoxib 25 mg) developed superficial venous thrombophlebitis. The event was not confirmed as serious cardiovascular thrombotic by the adjudication committee.*

1.4.5 Exposure

Although designed as a 3-month study, actual exposure was significantly shorter. Median exposure to both rofecoxib and naproxen was 84 days (mean was approximately 69 ± 30 days). Overall, most of the patients were compliant with dosing (88.8%). The percentage of patients with 80% compliance was similar in both treatment groups.

1.5 Safety Results

1.5.1 Overall safety

There was no overall advantage for rofecoxib 25 mg/d over naproxen 1000 mg/d. The numbers of patients with one or more adverse events (AE's), serious AE's, who died or discontinued due to an AE were similar in both treatment groups.

Table 6. NDA 21-042. ADVANTAGE study. Clinical Adverse Event Summary.

	Rofecoxib 25 mg/d (N= 2785)		Naproxen 500 mg b. (N= 2772)	
With one or more AEs	1814	(65.1)	1825	(65.8)
With serious AEs	68	(2.4)	72	(2. 6)
Who died	5	(0.2)	4	(0.1)
Who discontinued due to an AE	374	(13.4)	386	(13.9)

Source sponsor's table 21.

1.5.1.1 Deaths

There were 5 deaths in the rofecoxib group (0.2%) and 4 in the naproxen group (0.1%) (Table 7). Except for one 56-year-old patient who died of complications of gallbladder carcinoma, all patients were older than 70 years.

Four of the five deaths in the rofecoxib group were due to cardiovascular causes (three sudden death, one ruptured aortic aneurism). There were no cardiovascular deaths in the naproxen group. Of note, one patient with prior borderline renal function taking furosemide died of complications of acute renal failure in the naproxen group. None of the deaths were considered by the investigator to be drug-related. Narratives of deaths are presented in Appendix 1.

Table 7. Listing of Deaths in the ADVANTAGE study

AN/site	Age/ sex	Prior Medical History	Concomitant medications	Cause of death	Day #
Rofecoxib					
5005/065	73 F	HTN, ⌉lip, ⌋K	none	Sudden death	40
3700/200	74 M	DM, CAD, CABG, ⌉lip	**ASA, ACE(-), statin, glybur**	Sudden death	42
4856/210	71 F	-		Astrocytoma	120
4049/658	71 M	A fib, HTN, CAD, Hematuria	none	Sudden death	60
3423/679	75 F		digoxin, diltiazem none	Rupture aortic aneur	42
Naproxen					
1841/059	56 F	-	none	Gallbladder Ca.	120
7154/702	79 F	DM, HTN, anasarca	aleandronate, glypzide	Pancreatic Ca.	90
3105/777	74 F	HTN,CHF,depression, hyperuricemia, Cr. 1.5	verapamil, ACE(-), lasix, fluoxetine	Acute renal failure	40
7114/831	78 M	COPD, PVD, smoker	ASA	Lung Ca	60

Source: Advantage CSR.

Reviewer's comment:

Of note, the cause of death for patient # 065 5005 (on rofecoxib), had been listed by the investigator as hypertensive heart disease and ***not referred for adjudication*** *as a potential cardiovascular thrombotic event to the cardiovascular adjudication committee. The patient called her son complaining of chest pain and by the time the son arrived she was dead. In the opinion of this medical reviewer, the cause of death for this patient was sudden death, which would in fact meet criteria for cardiovascular thrombotic event.*

1.5.1.2 Serious AEs

A total of 140 patients - 68 (2.4%) in the rofecoxib group and 72 (2.6%) in the naproxen group - had at least one serious clinical AE during the study.

The findings of this large but relatively short study (3 months) with the rofecoxib 25 mg dose are consistent with those in the longer term (9-month) VIGOR study at the 50 mg dose. Again there is a lower number of digestive system related AE's in the rofecoxib group, but there is no overall advantage of rofecoxib over naproxen.

Table 8. Serious AE's occurring in two or more patients in ADVANTAGE.

	Rofecoxib 25 mg N= 2785 n %	Naproxen 1000 mg N= 2772 n %
Patients with at least one serious AE	68 (2.4)	72 (2.6)
Body as a whole	7 (0.3)	10 (0.4)
Cardiovascular system	23 (0.8)	17 (0.6)
Digestive system	7 (0.3)	21 (0.8)
Endocrine	1 (0.0)	1 (0.0)
Hemic and lymphatic	1 (<0.1)	2 (0.1)
Hepatobiliary system	3 (0.1)	1 (<0.1)
Musculoskeletal system	7 (0.3)	7 (0.3)
Nervous system	4 (0.1)	2 (0.1)
Psychiatric disorder	4 (0.1)	1 (0.0)
Respiratory system	6 (0.2)	5 (0.2)

(Source sponsor's table 24).

Reviewer's comment: Of note, the dose of rofecoxib used in this trial is half of the dose used in VIGOR but the dose of naproxen is the same (500 mg bid) in both trials. The incidence of serious adverse events in ADVANTAGE (2.4 and 2.6% in rofecoxib and naproxen respectively) is much lower than in VIGOR (9.3 and 7.8% in rofecoxib and naproxen respectively). This observation may be in part explained by the shorter duration of the study and the different population (OA in ADVANTAGE, RA in VIGOR).

A table of serious events that required hospitalizations is presented in Appendix 2. Again, there was no overall advantage of rofecoxib over naproxen. Twice the number of patients required hospitalization for GI related serious AE's in the naproxen group (5 and 12 for rofecoxib and naproxen respectively) and a numerically higher number of patients required hospitalization for CV related events in the rofecoxib group (18 and 13 on rofecoxib and naproxen respectively).

1.5.1.3 Serious AE's by ASA use

Table 9. ADVANTAGE study. Concomitant ASA use during study by dose*

	ROFECOXIB 25 MG N= 2785		NAPROXEN 1000 MG N= 2772	
	n	%	n	%
Low dose (20-325 mg/day)	**352**	**(12.7)**	367	(13.3)
Non-ASA user (<20 mg/day)	2425	(87.0)	2400	(86.5)
Other ASA user (>325 mg/day)	8	(0.3)	5	(0.2)

*** Categories defined by the sponsor for this study as follows: "Low dose": 20 to 325 mg/day; "Non user": Average of <20 mg/day or following a CV event; "Other": >325 mg/day or started therapy during study. Source: Table 10 Advantage CSR and response to request for information submitted by sponsor 6/29/01.**

Distribution of ASA use in the ADVANTAGE study is presented in Table 8. Analysis of serious AE's by ASA use demonstrated a similar incidence of events in the low aspirin users and non-users, except for the cardiovascular and the digestive system.

Table 10. Serious AE's by ASA use (events with incidence 0.5%), as reported by investigators.

	Rofecoxib N= 2785		Naproxen N= 2772	
	Non ASA users	Low dose ASA	Non ASA users	Low dose ASA
	N= 2422	N= 352	N= 2398	N= 367
	n (%)	n (%)	n (%)	n (%)
Patients with at least one event in any body system	54 (2.2)	14 (4.0)	59 (2.5)	12 (3.3)
Cardiovascular	16 (0.7)	7 (2.0)	14 (0.6)	2 (0. 5)
MI	3	2	1	-
Sudden death	2	1	-	-
Digestive system	5 (0.2)	2 (0.6)	18 (0.8)	3 (0. 8)

Source: Corrected Table 68 of Advantage CSR submitted 8/801).

Reviewer's comment:

In this short trial, the data suggest that co-use of low dose ASA increased the risk of serious GI events for rofecoxib (0.6%) but not for naproxen (0.8%, unchanged). The trial, however, was not designed to adequately assess the long-term effect of co-administration of ASA in the gastrointestinal system.

Most importantly, patients with known cardiovascular risk –as defined by patients using low dose prophylactic ASA - receiving rofecoxib had four fold more serious cardiovascular adverse events than those receiving naproxen (2.0% vs 0.5%).

In this three-month study with a dose of rofecoxib approved for chronic use in patients with OA, those on cardiovascular prophylaxis showed a trend towards more cardiovascular events (2.0 %) than those not on aspirin in the rofecoxib group (0.7%). Presumably, these patients are at higher cardiovascular risk than those not taking

aspirin, therefore the finding is not unexpected. However, this was not the case in the naproxen treatment group (0.5 % and 0.6 %, for those who were and were not on ASA, respectively).

The sponsor has speculated that the excess risk of cardiovascular thrombotic events in the rofecoxib group as compared to naproxen in the VIGOR study may be due to the lack of anti-platelet effect of rofecoxib and has proposed that addition of low dose ASA in high risk patients may prevent the problem. The limited data on rofecoxib and ASA use from the ADVANTAGE study suggest that low dose ASA in patients with prior cardiovascular history, might not eliminate the excess risk of serious cardiovascular events of rofecoxib compared to naproxen.

1.5.1.3 Dropouts due to adverse events

Table 11. ADVANTAGE. Dropouts due to adverse events

	Rofecoxib N= 2785 n %	Naproxen N= 2772 n %
Number of AE dropouts	**374 (13.4)**	**386 (13.9)**
Body as a whole	87 (3.1)	102 (3.7)
Cardiovascular	40 (1.4)	21 (0.8)
Digestive system	113 (4.1)	142 (5.1)
Endocrine	1 (0.0)	(0.0)
Eyes, ears, nose and throat	7 (0.3)	8 (0.3)
Hemic and lymphatic	1 (0.0)	2 (0.1)
Hepatobiliar system	2 (0.1)	1 (0.0)
Musculoskeletal system	45 (1.6)	49 (1.8)
Nervous system	30 (1.1)	24 (0.9)
Psychiatric disorder	14 (0.5)	7 (0.3)
Respiratory system	8 (0.3)	10 (0.4)
Skin and skin appendages	21 (0.8)	23 (0.8)

Reviewer's comment:

Consistent with the VIGOR study, there was no overall advantage of rofecoxib 25 mg/day over naproxen 1000 mg/day, based on the number of dropouts due to AE's. The percentages of dropouts due to AE's in the ADVANTAGE study are similar to those in VIGOR (15.9 and 15.8% for rofecoxib and naproxen, respectively). Of note, the number of dropouts due to cardiovascular related events was almost twice in the rofecoxib arm (n=40, 1.4%) when compared to the naproxen arm (n=21, 0.8%).

1.5.1.4 Most common adverse events

The total number of adverse experiences was approximately 65% in each treatment group. Adverse experiences by body system were generally also similar between treatment groups, including the digestive system (24% and 26 % in the rofecoxib and

naproxen arms, respectively). Again there was no overall advantage of rofecoxib 25 mg/day over naproxen 1000 mg /day.

1.5.1.5 Laboratory adverse events

Mean changes

Laboratory measurements were taken at baseline and at Week 12. Mean changes from baseline in each laboratory parameter were small and comparable between treatment groups, including hemoglobin, hematocrit, BUN, creatinine and liver function tests.

Serious Laboratory Adverse Experiences

Only one patient had a serious laboratory AE during the study. The event was moderately decreased hemoglobin. No action was taken with regard to study drug.

Discontinuations Due to Laboratory Adverse Experiences

Eleven patients (0.4%) in the rofecoxib group and 6 (0.2%) in the naproxen group, were withdrawn from the study due to a laboratory AE. None of them were serious.

1.5.1.6 Vital signs

Vital signs (diastolic and systolic blood pressure, heart rate, and respiration rate) were measured at each study visit. Mean changes and exceeding limits of change from baseline at week 6 and 12 were analyzed.

Maximum increases in systolic blood pressure at Week 12 were 94 mmHg and 60 mmHg for the rofecoxib and naproxen groups, respectively; **mean increases** were **1.04** mmHg and **0** mmHg in the rofecoxib and naproxen groups respectively. Maximum increases in diastolic blood pressure at Week 12 were 40 mmHg and 30 mmHg in the rofecoxib and naproxen treatment groups respectively; **mean increases** were **0.32** mmHg and **-0.66** mmHg in the rofecoxib and naproxen groups, respectively.

Defined limits of change for blood pressure were as follows: systolic blood pressure >140 mmHg with an increase from baseline >20 mmHg at either week 6 or 12; and diastolic blood pressure >90 mmHg with an increase from baseline >15 mmHg at either week 6 or 12.

Percentage of patients who exceeded the limit change for SBP at either week 6 or 12 were 10.7% and 9.1% for rofecoxib and naproxen, respectively. The percentage of patients who exceeded limits in SBP at both week6 and 12 were 2.3% and 1.6% in the rofecoxib and naproxen groups, respectively. Few patients in either treatment group (0.5%) had a change in diastolic blood pressure exceeding the defined limit at both visits.

Reviewer's comment: Patients in the rofecoxib group tended to have a larger increase in blood pressure compared to the naproxen group, although, in this three-month study, the differences in blood pressure changes were small.

1.5.2 Analyses of Cardiovascular Safety

1.5.2.1 Cardiovascular thrombotic events. Serious cardiovascular (CV) AEs occurring in a patient while on study treatment or within 14 days of discontinuation of study treatment were reviewed by the sponsor for inclusion in the adjudication process.

Of the 23 and 17 investigator reported serious CV AEs in the rofecoxib and naproxen arm respectively, 14 and 13 were considered by the sponsor to be thrombotic-related (as per Merck's Vascular SAE Terms Eligible for Case Adjudication, Appendix 3) and referred for blinded adjudication to the Cardiovascular Adjudication Committee. Two additional cases obtained through the WAES (Worldwide Adverse Event System) database were also referred for adjudication by the sponsor, making a total of **14 and 15** cases **referred** for adjudication from the rofecoxib and naproxen arms, respectively.

Reviewer's comment: The two cases referred for adjudication from the WAES database were not technically investigator reported events. It is unclear whether these cases represent unblinded data (both cases were on naproxen).

Investigator reported serious CV AEs are presented in the following table.

Table 12. Investigator reported Serious AE's related to the CV system by ASA use

	Rofecoxib			Naproxen		
	All N= 2785	No ASA N= 2425	ASA N=352	All N= 2772	No ASA N= 2400	ASA N= 367
	n %	events	events	n %	events	events
Any CV related event	**23 (0.8)**	**16 (0.7)**	**7 (2.0)**	**17 (0.6)**	**15 (0.6)**	**2 (0.5)**
Acute Myocardial Infarction	1	-	1	-	-	-
Arterial Oclusion	1	1	-	-	-	-
Arterial rupture	1	1	-	-	-	-
Atherosclerosis	1	1	-	1	1	-
Atrial fibrillation	2	2	-	1	-	1
Cardiac arrest	-	-	-	1	1	-
Cardiovascular disorder	1	-	1	-	-	-
Carotid artery obstruction	1	-	1	-	-	-
Cerebellar hemorrhage	-	-	-	1	1	-
Cerebral aneurysm	1	1	-	-	-	-
Cerebral infarction	-	-	-	1	1	-
Cerebrovascular accident	-	-	-	3	3	0
Congestive heart failure	4	3	1	2	2	-
Coronary artery disease	2	1	1	2	1	1
Deep venous thrombosis	-	-	-	3	3	-
Hypertension	1	1	-	-	-	-
HTN heart disease	1	1	-	-	-	-
Myocardial infarction	3	2	1	1	1	-
MI- age indetermined	1	-	1	-	-	-
Non-Q wave MI	1	1	-	-	-	-
Pulmonary edema	1	1	-	-	-	-
Sick sinus syndrome	1	1	-	1	1	-
Subarachnoid hemorrhage	1	1	-	-	-	-
Supraventricular tachycardia	1	1	-	1	1	-
Third degree AV block	1	-	1	-	-	-
Thrombophlebitis	1	-	1	-	-	-
Transient ischemic attach	2	2	-	2	2	-
Unstable angina	1	1	-	-	-	-
Vasospasm	1	1	-	-	-	-
Ventricular fibrillation	-	-	-	1	1	-
Ventricular tachycardia	1	-	1	-	-	-

(Source: sponsor's tables 60, 68 & 69, corrected tables submitted 8/8/01). (N= patients randomized; n= patients with events). This list does not include two additional cases obtained though WAES.

Reviewer's comment: The incidence of investigator related serious CV AEs was higher among those patients taking concomitant aspirin in the rofecoxib group. The subgroup of patients taking aspirin presented four fold more serious CV adverse events in the rofecoxib group than the naproxen group.

1.5.2.2 Adjudicated serious CV/thrombotic events.

Each clinical event referred for adjudication was reviewed blindly by three cardiologists (CV adjudication committee). The criteria for adjudication of cardiovascular serious thrombotic events were the same as the ones used in the VIGOR study.

Table 13. Criteria for Adjudication of Cardiovascular Serious Thrombotic events

a. Coronary – *Cardiology*

1. Acute MI (fatal or non-fatal)
    a. Spontaneous
    b. Secondary to an antecedent stressor (major surgery, GI bleed)
    c. Complication of PTCA or coronary revascularization procedure
2. Unstable angina pectoris
3. Cardiac (atrial or ventricular thrombus)
4. Resuscitated cardiac arrest (without identified cause listed elsewhere)
5. Sudden or unexplained death

b. Peripheral (other than cardiac or cerebrovascular*)* vascular – *Peripheral Vascular*

1. Pulmonary embolism (fatal or non-fatal)
    a. Spontaneous
    b. Secondary to an antecedent stressor
2. Peripheral venous thrombosis
    a. Spontaneous
    b. Secondary to an antecedent stressor
3. Peripheral arterial thrombosis/thromboembolism (fatal or non-fatal)

c. Cerebrovascular – *Neurology*

1. Ischemic cerebrovascular stroke (fatal or non-fatal) with adequate documentation to subclassify as follows:
    a. Large-artery atherosclerosis
    b. Cardioembolism
    c. Small-artery occlusion (lacune)
    d. Other determined etiology
2. Ischemic cerebrovascular stroke (fatal or non-fatal) without adequate documentation to subclassify etiology
3. Hemorrhagic cerebrovascular stroke or hemorrhagic change (fatal or non-fatal)
4. Transient ischemic attack
5. Cerebrovascular venous thrombosis (fatal or non-fatal)

d. Non-Thromboembolic event

The SOP for this adjudication of cardiovascular events seem appropriate to FDA reviewers. The SOP includes a summary of the available data used by the committee and guidelines on the interpretation of cardiac data (e.g., how to interpret an elevated CPK-MB or an abnormal ECG).

Table 14. Listing of events referred for adjudication and adjudication results

Site/ Allocation Age/sex/ Treatment	Prior Hx/ CV risk factors	Low dose ASA	*Adjudication*	
0064 4746 54M *R*	HTN	Yes		Non fatal MI
0126 2401 70F *R*	COPD, varicose ve	No	No	Superficial thromboflebitis
0193 5751 78F *R*	DM, CAD	No	**Y**	Unstable angina
0200 3700 74M *R*	CAD, CABG	Yes	**Y**	Sudden death
0212 1955 70F *R*	Atrial fib	No	No	Aneurism. Subarachnoid hemorr
0215 4378 72F *R*	↑Lipid, CVA, ERT	Yes	No	Non thromboembolic*
0357 0047 69M *R*	IBS, Peyronie's	No	**Y**	Non fatal MI
0644 2176 79M *R*	↑Lipid, HTN, PVD	Yes	**Y**	Non fatal MI
0658 4049 71M *R*	HTN, CAD, Afib	No	**Y**	Sudden death
0760 3253 72F *R*	HTN, hypothyroidism	Yes	No	Non thromboembolic event
0810 6272 76M *R*	HTN, CAD	No	**Y**	TIA. (w/Ventricular thrombus)
0821 5108 72M *R*	↑Lipid, HTN,DM	No	**Y**	Non fatal (Non Q wave) MI
0831 5382 70M *R*	HTN, angina	No	**Y**	Non fatal MI
0002 9009 60M *R*	↑Lipid, HTN, SyndrmX	Yes	No	Non thromboembolic*
0016 9145 71F N	DM	No	**Y**	TIA
0187 0665 60M N	-	No	**Y**	Non fatal MI
0283 2182 58F N	? Hx of CVA , ERT	Yes		Ischemic CVA (no subclassif)*
0314 1477 70M N	CAD, HTN	No	No	Non thromboembolic
0340 6823 67M N	CAD,HTN, DM	No	No	Worsening CHF
0386 3155 77F N	↑Lipid, HTN,DM	No	**Y**	Ischemic CVA, small artery occlus*
0408 4129 54M N	**CAD,CABG, HTN**	Yes	**Y**	Unstable angina
0443 1418 45F N	↑Lipid, DM	No	**Y**	Unstable angina
0449 4783 70F N	HTN, depression, ERT	No	**Y**	Deep venous thrombosis
0462 1867 84F N	DM, postop per, ERT	No	**Y**	Deep venous thrombosis**
0521 5761 58F N	HTN, ERT	No	**Y**	Cerebral infarction
0580 6099 80M N	↑Lipid, HTN	No	**Y**	Ischemic CVA
0614 2792 74M N	HTN, prostatic ca.	No	**Y**	Deep venous thrombosis
0702 6480 59F N	Cerebral hemorr, ERT	No	Y	Ischemic CVA
0774 3189 66F N	HTN, CAD, MI, ERT	No	**Y**	Ischemic CVA
0065 5005 73F *R*	↑Lipid, syst mumur	No	-	Sudden death***

Source: Advantage CSR, CV adjudication package. R: rofecoxib. N: naproxen. CAD: coronary artery disease. HTN: hypertension, DM: diabetes mellitus. ERT**:** Estrogen replacement therapy. * FDA reviewers do not agree with adjudication. ** Occurred outside window determined by SOP and should have not been referred for adjudication. *** Not referred for adjudication.

Results of the adjudication:

Of the 29 cases evaluated by the CV adjudication committee (14 and 15 in the rofecoxib and naproxen groups respectively), seven were considered non-thrombo-embolic events, resulting in 9 and 12 adjudicated serious CV/thrombotic events.

1.5.2.3 Review of serious CV events by FDA reviewers.

Reviewer's comment:

- *The referral for adjudication of two additional cases obtained from WAES - not reported by the investigators as cardiovascular thrombotic events - is of concern. One of these cases was adjudicated by the CV adjudication committee (102 462 1867, DVT on naproxen). However, a hand written note in the CRF for this case states that it is not known whether the patient ever took the assigned medication because she did not return the diary. As per the sponsor's June 22, 2001 correspondence, the event occurred more than 14 days after discontinuation of study drug. The SOP establishes a 14-day window period. Therefore, this case should have never been referred for adjudication.*

- *One cardiovascular death that should have been referred for adjudication was not referred because the term used by the investigator was not in the list of potential cardiovascular thrombotic events (hypertensive heart disease). This case was actually a case of sudden death (102 065- 5005, on rofecoxib). See Appendix 3a ("Terms eligible for adjudication").*

- *Post-hoc determination of the 'thrombotic' nature of some of these events may be difficult. Final interpretation of some data – often limited data - is by necessity, somewhat subjective. The Medical Officer assigned to this NDA reviewed all adjudication packages. For those cases in which the MO did not agree with the committee, adjudication packages were provided to the Divisions of Cardio-Renal and Neuropharm products. Two different FDA reviewers disagreed with the adjudication of four cases (0215 4378 211 and 0002 9009 308, on rofecoxib; and 0386 3155 209 and 0283 2182 222 on naproxen).*

Table 15. Cases for which FDA reviewers disagree with the results of CV adjudication committee*.

Patient	Treatment	Adjudication Committee	CVT	FDA reviewers	CVT
0215 4378	Rofecoxib	Non-thromboembolic	N	Ischemic CVA	Y
0386 3155	Naproxen	Ischemic CVA, small artery occlusion	Y	Unable to adjudicate, Chorea of unknown etiology	N
0283 2182	Naproxen	Ischemic CVA	Y	Unable to adjudicate	N
0002 9009	Rofecoxib	Non-thromboembolic	N	Unstable angina	Y
0462 1867	Naproxen	DVT	Y **	Out of adjudication period	N
0065 5005	Rofecoxib	Death due to HTN	***	Sudden death	Y

*Re-adjudication based on review of cases by reviewers from HFD-550, HFD-110 and HFD-120). CVT: serious cardiovascular thrombotic event. * Narratives are presented in Appendix 4. ** It should not have been referred for adjudication. *** It was not referred for adjudication.*

Table 16. ADVANTAGE: Summary CV Thrombotic events as presented by the sponsor (adjudicated by CV Adjudication Committee) and FDA re-adjudicated events.

	Number of patients with CV Committee adjudicated serious CV-thrombotic events		Number of patients with FDA re-adjudicated serious CV-thrombotic events	
	Rofecoxib (N= 2785)	Naproxen (N= 2772)	Rofecoxib (N= 2785)	Naproxen (N= 2772)
	9	12	12	10
Cardiac	**8**	**3**	**10**	**3**
Sudden death	2	0	3	0
MI	5	1	5	1
Angina	1	2	2	2
Cerebrovascular	**1**	**7**	**2**	**5**
CVA	0	6	1	4
TIA	1	1	1	1
Peripheral	**0**	**2**	**0**	**1**
DVT/thromboflebit	0	2	0	1

There were **10 cardiac** events in the **rofecoxib** arm compared to **3** in the **naproxen** arm**.** Eight of the 10 cardiac events in the rofecoxib arm (5 MI, 2 sudden deaths, one angina) were in males; two additional cardiac events were in women. The cardiac cases in the naproxen arm were 2 unstable angina (1 man, 1 woman) and one MI (in a man with no prior CV history). Most of the cardiac events were in patients older than age 60, with known risks factors for CAD such as hypertension, diabetes, hyperlipidemia or prior history of CAD. Five of the ten cardiac events were in patients taking ASA. The number of events is small to allow interpretation regarding distribution of events in ASA users and non users.

*Reviewer's comment: A trend towards an excess of **cardiac events** in the rofecoxib 25 mg group in this 12 week study is noted. This observation is consistent with the pattern seen in VIGOR.*

Of note, there were 2 and 5 cerebrovascular thrombotic events in the rofecoxib and naproxen arm, respectively, as adjudicated by the FDA Neuropharm reviewer. Two of the four CVA's were in patients taking hormonal replacement therapy. The reason for a lack of consistency between VIGOR and ADVANTAGE in regards to the risk of CVA's is unclear. It may be that cardiac and cerebrovascular events are different entities. However, the lack of power in the ADVANTAGE study may be an explanation.

A summary of the sponsor analyses of serious investigator reported CV events, adjudicated serious cardiovascular thrombotic and APTC (Anti Platelet Trialist's Collaboration) endpoints is presented in Appendix 3b. While the 95% CI's cross, the trend is consistent with FDA review for cardiac events.

The number of events is small, however, the finding is concerning because:

1. *This is only a three month study.*
2. *The dose of rofecoxib is 25 mg a day, the approved dose in OA (not twice the dose, as in VIGOR),*
3. *The OA population is known to have lower cardiovascular risk than the RA population.*

The study is of extremely short duration to evaluate the cardiovascular effect of a drug in the prevention or increased risk of MI and stroke. Studies designed to evaluate cardiovascular outcomes are usually of 3-4 years duration.

1.5.3 NSAID-related events. The sponsor provided analyses of pre-specified NSAID-related adverse events similar to the ones that had been done in the VIGOR study.

1.5.3.1 NSAID-related adverse events related to edema, HTN and CHF

In this short-term, 12-week study, more patients had CHF related events and discontinued due to edema-related and HTN-related events in the rofecoxib 25 mg/day group than in the naproxen 1000 mg/day group.

Table 17. ADVANTAGE study. NSAID-related adverse events related to edema[1], hypertension[2] and congestive heart failure[3].

	Rofecoxib N= 2785 n %	Naproxen N= 2772 n %
Patients with Edema-related events	151 (5.42)	135 (4.87)
discontinued due to Edema related event	19 (0.68)	12 (0.43)
Patients with HTN related event	90 (3.23)	72 (2.59)
discontinued due to HTN related event	15 (0.54)	7 (0.25)
Patients with at least one CHF-related event	11 (0.39)	6 (0.22)

(Source Table 73, 74, 75 and appendix 4.1.57, Advantage CSR). Note: patients with two or more adverse events within a body system is counted only once within a body system. [1] Includes terms such as edema, peripheral edema and lower extremity edema. [2] Includes terms such as blood pressure increased, diastolic hypertension, systolic hypertension, labil hypertension, hypertension, uncontrolled hypertension.

Of the discontinuations due to edema-related events, only one patient (AN 1757, rofecoxib) was considered to have a serious event. The patient, a 72 year old male with

history of HTN, DM, CAD, hyperlipidemia and CABG developed anasarca and was hospitalized approximately on treatment day #40. The physician indicated that the *patient lost about 30 pounds of fluid* with diuretic therapy during hospitalization.

CHF related events were defined as either congestive heart failure or left ventricular failure. Of the CHF related events, six were considered to be serious by the investigator: four in rofecoxib (AN 0085, 1082, 7389, 5108) and two in naproxen (6823 and 6398). Patient 5108 (a 72 year-old male) had a non-Q wave MI.

> *Reviewer's comment: The number of events is relatively small but despite the short duration of treatment and the fact that this is the 25 mg dose, the trend is consistent with findings in the VIGOR study.*

1.5.3.2 Renal safety

There was one case of acute real failure (AN 3105/777) in the naproxen arm, and one case of acute tubular necrosis (AN 1332/537 in the rofecoxib arm).

Twice the number of patients presented increased serum creatinine and BUN in the rofecoxib compared to the naproxen arm, respectively. Only one patient (in the naproxen arm) required discontinuation due to increased creatinine.

Table 18 Renal related Laboratory AE experiences

	Rofecoxib N=2785 n (%)	Naproxen N=2772 n (%)
Blood urea nitrogen increased	15 (0.5)	7 (0.3)
Serum creatinine increased	21 (0.8)	10 (0.4)

1.5.3.3 Liver safety

There were two discontinuations due to liver-related clinical or laboratory adverse events, one in each treatment arm.

1.5.3.4 GI safety

The sponsor defined primary endpoint for this study was the cumulative incidence of discontinuations due to GI AE and abdominal pain at end of study endpoint.

The sponsor conducted a post-hoc analysis of PUBs (perforation, symptomatic ulcers and bleedings) similar to the analysis conducted for the VIGOR study. Of all the serious AE related to the digestive system, 6 and 12 events were referred to the GI adjudication committee from the rofecoxib and naproxen arms, respectively. Of those, 2 and 9 were confirmed PUBs by the adjudication committee. Of the confirmed PUBs, one was complicated in the rofecoxib group (the patient was taking ASA) and

four were complicated in the naproxen group (one patient was taking ASA). The number of cases is small but the trend is consistent with the findings in VIGOR.

Reviewer's comment: The study succeeded in the sponsor's defined primary endpoint. However, this endpoint is not of clinical significance unless it is consistent with the overall safety profile, including cardiovascular events which are highly morbid. Only 7 of the 113 and 21 of the 142 discontinuations due to digestive symptoms were considered serious adverse events in the rofecoxib and naproxen arm respectively. Five of the 7 and 12 of the 21 serious digestive AE's required hospitalization in the rofecoxib and naproxen arm, respectively. Two of the seven and 3 of the 21 serious digestive AE's were on patients using concomitant aspirin in the rofecoxib and naproxen arm, respectively.

2.0 Safety Update Report (SUR)

2.1 Overall Safety.

The Complete SUR was submitted to the Agency in July 12, 2001. This report includes the safety update of the extension studies in the original OA program (029, 058, 034 and 035), studies 083 (bone mineral density), 120 and 121 (low back pain), 118 (prostatitits pain), 903 (OA) and 078, 126 and 091 (prevention of Alzheimer's). The SUR, however, does not contain the complete study reports for these studies.

Table 19. Studies included in Safety Update Report

Study/protocol #	Duration	Dose of rofecoxib	Patients randomized*		
			Rofecoxib	Placebo	Active control
Extension to Original NDA OA studies					
034, 035	some patients up to >2 years	12.5 mg 25 mg 50 mg	415 **(1)** 475 78	-	409 Diclofenac **(1)**
Elderly— 058	Some patients up to 2 years	12.5 mg 25 mg	46 25	-	36 Nabumetone
New completed trials					
Bone Density— 083	Up to 65 weeks	25 mg	136	100	148 Ibuprofen **(1)**
Alzheimer's Disease— 091	Up to 479 days	25 mg	346 **(14)**	346 **(8)**	-
Chronic Prostatitis— 118	6 weeks	25 mg 50 mg	53 49	59	-
Chronic Low Back Pain— 120/121	4 weeks	25 mg 50 mg	232 233	228	-
OA Versus Naproxen — 901	6 weeks	12.5 mg	471 **(1)**	-	473 Naproxen
OA Versus ARTHROTEC — 902	6 weeks	12.5 mg	453 **(1)**	-	456 (Diclofenac/ misoprostol)
New ongoing trials					
Alzheimer's Disease— 078	Up to 1052 days	25 mg	721 **(15)**	729 **(9)**	-
Alzheimer's Disease— 126	Up to 430 days	25 mg	381 **(4)**	376 **(3)**	-

* Patients randomized (Few patients were actually exposed to 2 years in the extension to the original NDA). The number of patients who died for any cause are in parenthesis. Source: modified from sponsor's table 1 of the SUR submitted 7/12/01 and data on deaths from individual studies.

2.1.1 Deaths in the SUR.

There were a total of 58 deaths in the SUR. The number of deaths appears in parenthesis in Table 17.

Two deaths occurred during the extension period of the original NDA OA studies (029,034,035, 058):

- AN 8353, 64 M on rofecoxib 12.5 mg (post-op complication after CABG, day 607 of therapy)
- AN 5568, study 034: 75 F on diclofenac 150 mg, day 719 (post-op complication of hip replacement).

The total number of deaths in the entire original NDA and extensions was: 4 on rofecoxib 12.5 mg, one on rofecoxib 50 mg (in a patient with RA), one on naproxen, one on nabumetone and 9 deaths in the diclofenac group. For more detailed review the reader is referred to the MO review of NDA 21-042.

One death occurred in each of the remaining protocols submitted in this SUR:

- AN 0063, (protocol 083) a 60-year-old white woman with a history of hypertension and obesity was found dead in bed approximately 5 months into receiving ibuprofen 800 mg TID.
- AN 2301, (protocol 901) a 55 year old woman with history of chest pain and palpitations was found dead in bed 4 days after taking rofecoxib 12.5 mg a day. Autopsy showed coronary artery disease.
- AN 1659 (protocol 902), a 94-year-old man (AN 1659) on rofecoxib 12.5 mg for 15 days committed suicide by putting a plastic bag over his head.

Fifty-three of the 58 deaths were in the Alzheimer's studies: 33 on rofecoxib 25 mg and 20 on placebo (see below). Excluding the Alzheimer's studies, the number of deaths were small and do not raise additional safety concerns.

2.1.2 Serious AE's and Discontinuations due to AE's in the SUR

The pattern of SAE's and discontinuations due to AE's in the SUR was consistent with that observed in the original NDA. Of note, except the Alzheimer's studies most of these studies were of small size and short duration.

2.2 Alzheimer's studies

Of all the data submitted in the SUR, the three studies for prevention of Alzheimer's disease potentially provide the most valuable information about long term exposure to rofecoxib 25 mg in comparison to placebo. However, limited safety data has been supplied from these studies. At the time of the submission of the SUR, study 091 had been completed; study 078 was ongoing and the data were not frozen by the cutoff date for the SUR (April 2001); study 126 had been terminated early (March 2001) and full report was not available. The SUR included listing of serious fatal and nonfatal AE's from the three studies as well as adjudication packages of all serious potentially cardiovascular thrombotic events referred for adjudication to the CV adjudication committee. In subsequent submissions, at request of FDA reviewers, listing of discontinuations due to AE's and analyses of HTN, edema and CHF related events were provided.

Protocol 091 was a placebo-controlled, parallel-group, multicenter, 15-month double-blind study to evaluate the efficacy and safety of rofecoxib 25 mg to slow the progression of symptoms of Alzheimer's Disease. Patients of either gender who were $\geq$50 years of age with possible or probable Alzheimer's Disease were eligible to participate. Patients using NSAIDs for $\geq$7 days/month for the 2 months immediately prior to entry were not eligible. Patients were excluded if they were living in a nursing home or skilled nursing facility. Eligible patients were randomized to rofecoxib 25 mg or placebo for 12 months. This was followed by an additional 3-month treatment phase in which 90% of the patients initially assigned to rofecoxib were treated with placebo while the other patients remained on their initial treatment. Safety and tolerability were assessed at each visit (screening, Months 1, 3, 6, 9, 12, 13.5, and 15).

Protocol 078 This is a placebo-controlled, parallel-group, double-blind, multicenter study to evaluate the effects of rofecoxib 25 mg on the prevention of Alzheimer's Disease and cognitive decline in patients $\geq$65 years of age with mild cognitive impairment. Eligible patients were randomized to receive rofecoxib 25 mg or placebo for 2 years or until 220 cases of clinically diagnosed probable or possible Alzheimer's Disease are observed, whichever comes later. Safety and tolerability were to be assessed at all visits.

Study 126 was similar in size and design to study 091.

As per the sponsor's listings the demographic characteristics, co-morbid conditions and concomitant medications were similar in both treatment groups in each study. The mean age of these patients was 75 years and the number of patients included in each study per treatment arm was approximately 370 for study 091 and 126, and approximately 700 for study 078.

The Alzheimer's studies specifically excluded patients at high cardiovascular risk. The following are some of the exclusion criteria used in the Alzheimer's studies (protocol 078):

1 Patient with a history (within 2 years) or current evidence of major stroke, multiple lacunar infarcts or transient ischemic events.
2 Patient with a history of angina or congestive heart failure with symptoms at rest.
3 Patients with a history of myocardial infarction or coronary artery bypass grafting, angioplasty, or stent placement within 1 year prior to study start.
4 Patients taking the following medications:
   - Warfarin, heparin, ticlopidine.
   - NSAIDs (including salicylates or other aspirin-containing compounds) on a chronic basis (defined as =7 total days out of the last 30 days for 2 consecutive months prior to potential study entry).
   - Estrogen replacement therapies (excluding topical cream preparations)

At some point, patients on warfarin were made eligible for the study, provided that there was an increased frequency of monitoring of prothrombin time after initiation of blinded study therapy (amendment 78-02). In a later amendment, done after enrollment was complete, patients *who developed a need for cardio-protective doses of aspirin while in the trial* were permitted to use aspirin up to 100 mg/day(78-06).

Exposure

The following tables were presented by the sponsor in the SUR (July 12, 2001):

Table 20 (a, b and c). Patient exposure in Alzheimer's studies.

Number of Days on Therapy by Treatment—Protocol 091

	Treatment		
	Rofecoxib 25 mg/ Rofecoxib 25 mg	Rofecoxib 25 mg/ Placebo	Placebo/ Placebo
N	35	311	346
Mean	355.7	340.8	365.7
Range (min to max)	461 (2 to 463)	479 (1 to 480)	475 (1 to 476)

Number of Days on Therapy by Treatment—Protocol 078

	Treatment	
	Rofecoxib 25 mg	Placebo
N	721	729
Mean (SD)	500.16 (276.60)	549.50 (271.06)
Range (min to max)	1052 (0 to 1052)	1039 (0 to 1039)

Number of Days on Therapy by Treatment—Protocol 126

	Treatment	
	Rofecoxib 25 mg	Placebo
N	381	376
Mean (SD)	155.96 (94.90)	161.84 (95.68)
Range (min to max)	349 (1 to 350)	429 (1 to 430)

Reviewer's comment: As noted in the above tables, mean exposure to rofecoxib 25 mg in 346 patients in study 091 was 348.25 days (standard deviation not provided), with a range of one to 480 days. Mean exposure to rofecoxib 25 mg in 721 patients in study 078 was 500 days (± 276 days) with a range of 0 to 1052 days of treatment. Mean exposure to rofecoxib 25 mg in 381 patients in study 126 was 156 days (±95 days) with a range of one to 350 days of treatment. The sponsor has not provided median time of exposure in each of the trials but has provided patient years at risk (see table below).

Table 21. Alzheimer's studies. Exposure to rofecoxib and placebo.

	Rofecoxib 25 mg		Placebo	
	Randomized	Pt. Years at risk	Randomized	Pt. Years at risk
091	346	301	346	366
078	721	996	729	1098
126	381	165	376	169
Total	1448	1461	1451	1634

Source: sponsor's table. SUR.

2.2.1 Overall Safety in the in Alzheimer's studies

2.2.1.1 Deaths

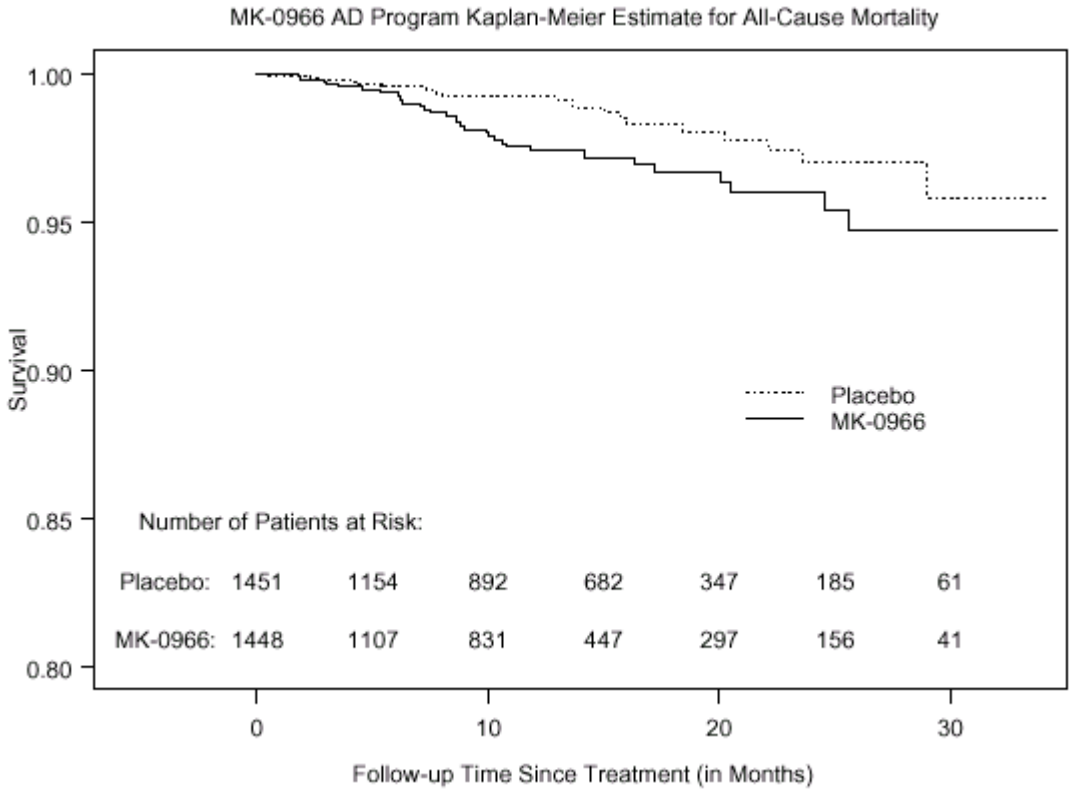
Pooled data from the three Alzheimer's studies showed that all cause mortality was higher in the rofecoxib 25 mg group, as compared to placebo (33 and 20 respectively). The p-value for the crude rate comparison between rofecoxib and placebo was 0.07. Of all deaths, 9 and 4 were confirmed as cardiovascular thrombotic by the CV adjudication committee.

Table 22. Deaths in Alzheimer's studies

Study #	Rofecoxib 25 mg N= 1448		Placebo N= 1451	
	n/Pt Years of exposure		n/Pt Years of exposure	
091	15/301		8/366	
078	14/996		8/1098	
126	4/165		3/169	
	n	(%)	n	(%)
Total*	33	(2.3)	20	(1.4)
CVT[1]	8	(0.6)	4	(0.3)
Other[2]	24	(1.7)	16	(1.1)

N= patients randomized. n= number of deaths. (%) crude rate. * P=0.007. [1]CVT: cardiovascular thrombotic death. Includes sudden death, myocardial infarction and ischemic cerebrovascular events confirmed as cardiovascular thrombotic by the CV adjudication Committee. [2] Other: Includes death associated with malignancy, sepsis, trauma, CHF/pneumonia, pulmonary embolism, hemorrhagic stroke, unclassified cause of death.

Figure 1. Kaplan Meier estimates. All Cause Mortality in the Alzheimer's studies.



The p-value for the logrank comparison between rofecoxib 25 mg and placebo = 0.026. (Source of Kaplan Meier curve: provided by Sponsor on 11/12/01)

> *Reviewer's comment: Listing of the cause of death in all patients in Alzheimer's studies is presented in Appendix 6. Of note, the trend is consistent in study 091 and 078. Study 078 is still ongoing. The sponsor has reported that study 126 was terminated early because of lack of efficacy in study 091 (Information submitted 11/26/01).*

2.2.1.2 Serious Adverse events in Alzheimer's studies.

Review of Serious Adverse events from the pooled Alzheimer's studies did not show major differences in all serious AE's, serious cardiovascular thrombotic events or serious digestive system events between rofecoxib and placebo.

Table 23. SUR. Summary of Serious AE's in Alzheimer's studies.

	Rofecoxib 25 mg N=1448 n (%)	Placebo N=1451 N (%)
Patients with at least one event	**261 (18.0)**	**260 (17.9)**
Body as a whole	70 (4.8)	55 (3.8)
CV AE's	77 (5.3)	82 (5.7)
Digestive AE's	40 (2.8)	32 (2.2)
Musculoskeletal	37 (2.6)	29 (2.0)
Skin and Appendices	20 (1.4)	42 (2.9)

Reviewer's comment:

There was a slightly higher number of serious digestive events in the rofecoxib group (2.8%) as compared to the placebo group (2.2%). These events included 2 gastric ulcers, 5 GI bleeding, 1 GI perforation, 2 hemorrhagic duodenal ulcer, 4 hemorrhagic gastric ulcer in the rofecoxib arm (N=12) and 1 GI bleeding, 2 GI perforation, 2 hemorrhagic gastric ulcer in the placebo arm (N=5) in the placebo arm. Of note, these are investigator reported terms, not confirmed events.

There was a slightly lower number of reported serious CV events in the rofecoxib group (5.3%) as compared to the placebo group (5.7%).

Discontinuations due to AE's were provided by the sponsor only for study 091. In this study of approximately 300 patients per treatment arm, there were differences in the digestive system (4.2 and 1.4% for rofecoxib and placebo respectively); respiratory system (2.3 and 0.3%) and urogenital system (1.9 and 0% had renal insufficiency) in the rofecoxib and placebo group, respectively.

2.2.2 Cardiovascular Safety in Alzheimer's studies

2.2.2.1 Cardiovascular thrombotic events referred for adjudication.

There was no substantial difference in the number of investigator reported serious cardiovascular potentially thrombotic events referred for adjudication between rofecoxib (n= 81) and placebo (n= 76). (Source: listing of serious CV thrombotic events referred for adjudication , submitted 9/6/01).

Reviewer's comment: By looking at the list of events referred for adjudication in the Alzheimer's studies it appears that the sponsor took a very conservative approach by referring all deaths, including terms such as "hepatic carcinoma" or "pulmonary fibrosis". However, even if only terms included in the original "Vascular SAE Terms Eligible for Case Adjudication" (Appendix 3a.) were

included, the number of patients with events was not substantially different: 62 and 60, in the rofecoxib 25 and placebo groups, respectively. Of those, the sponsor reports that 22 and 30 were considered adjudicated APTC events in the rofecoxib and placebo groups, respectively.

The size of the database is relatively small to detect differences in cardiovascular safety. The three Alzheimer's studies all together had approximately 1500 patients on rofecoxib 25 mg and 1500 on placebo. As per calculations made by FDA statisticians and presented at the February 8, 2001 AAC meeting, based on the cumulative data of serious CV thrombotic events observed in VIGOR, at least 2500 patients would be needed in each treatment group to detect statistically significant differences between treatments, if they existed at the same rate as presented in VIGOR.

Of note, although the studies included an elderly population (mean age 75 years), patients with high cardiovascular risk such as those with a recent history of myocardial infarction and stroke, and patients taking estrogen replacement therapy were excluded from the Alzheimer's studies. Studies specifically designed to evaluate cardiovascular effects (e.g. protective effect of a drug in the risk of myocardial infarction or stroke) usually involve thousands of patients for several years.

The Alzheimer's studies showed a trend towards an excess of cardiovascular deaths in the rofecoxib 25 mg group: 8 and 4 confirmed cardiovascular thrombotic deaths, in the rofecoxib 25mg and placebo groups, respectively. The Division of Cardio-Renal drug products has been consulted for detailed evaluation of potential cardiovascular thrombotic events in the Alzheimer's database. Results are pending at the time of this review.

Data provided with the Alzheimer's studies do not cancel out the findings in the VIGOR and ADVANTAGE studies.

2.2.2.2 Hypertension-related, edema related and CHF related events

At the reviewer's request, the sponsor provided data on hypertension, edema and CHF related events in studies 091 and 126 (submitted 10/1/01). Data from study 078 were not available because this study is still ongoing and blinded.

Table 24. SUR. Summary of HTN, edema and CHF-related events in Alzheimer's studies 091 and 126.*

	Rofecoxib 25 mg N= 726 n (%)	Placebo N= 722 N (%)
HTN-related	63 (8.7)	19 (2.6)
Edema-related	21 (2.9)	6 (0.8)
CHF-related	16 (2.2)	6 (0.8)

* Nine patients discontinued rofecoxib therapy due to the above AE's (3 in each category). One patient discontinued placebo due to a HTN- related event.

Reviewer's comment: consistent with prior databases, rofecoxib 25 mg is associated with higher incidence of hypertension, edema and CHF related events than placebo.

2.3 Short term placebo controlled studies in the SUR.

As part of the SUR, at the Agency's request, the sponsor provided data from five recently completed short term (4-6 weeks) studies that compared rofecoxib to placebo or other NSAIDs not included in the initial ADVANTAGE SUR. Three of these studies were placebo controlled (112, 116 and 905). In these studies, involving 456, 947 and 317 patients in the rofecoxib 12.5, rofecoxib 25 mg and placebo treatment arms respectively, four patients presented serious cardiovascular thrombotic events (one myocardial infarction and three coronary artery disease events), all in the rofecoxib 25 mg group.

The size and duration of these studies is too small to assess cardiovascular safety differences, however, the data suggest an increased risk in the rofecoxib 25 mg group as compared to placebo.

3.0 Safety from the RA efficacy studies (21-042/s012).

This is the summary of a preliminary safety review of the RA efficacy application. A more detailed review is presented in a separate review (NDA 21-042/s012).

The protocols included in the RA efficacy application had a complicated design, with some patients switching treatments between parts. The RA safety database contains approximately 2000 patients exposed to rofecoxib (12.5, 25 and 50 mg); 550 patients exposed to naproxen and 1000 patients exposed to placebo. The bulk of the exposure was to 3 and 6 months of treatment. Approximately 1500 patients were randomized to rofecoxib 25 mg (n= 797) and 50 mg (n= 677) in 3-month placebo controlled studies. Approximately 180, 140 and 80 patients were exposed to rofecoxib 25mg, rofecoxib 50mg and naproxen 1000 mg respectively, for one year or more.

3.1 Overall safety in the RA application database

There were a total of six deaths: four on rofecoxib, one on naproxen and one on placebo. None of the deaths were considered by the investigator to be treatment related. None of them were cardiovascular deaths.

The pattern of adverse events, discontinuations due to adverse events, laboratory AE's and vital signs was consistent with data submitted in the original NDA submission.

3.2 Cardiovascular safety in the RA application database.

3.2.1 Investigator reported serious cardiovascular thrombotic events

The risk of developing serious cardiovascular thrombotic events with rofecoxib 50 mg in the RA application safety database is higher than with naproxen (2.6 vs. 1.5 per 100 patient years). The findings are consistent with the VIGOR study. The cardiovascular risk for the 25 mg dose (2.2 per 100 patient years) is also higher risk than naproxen. Risk comparisons to the rofecoxib 12.5 mg and placebo groups is inadequate because of the difference in exposure.

Table 25. RA database. Summary of Investigator Reported Serious CV thrombotic events and Adjudicated events.(mostly 3-6 mo. studies, some patients exposed up to 3 years; placebo-controlled studies were only 3 months duration).

Treatment	Investigator reported serious CV thrombotic	Patient-years at risk *	Risk per 100 pt years	Adjudicated events	Risk per 100 pt years
Studies 096, 097, 098 and 103 (pivotal and endoscopic)					
Placebo	2	160	1.3	1	0.5
Vioxx 12.5	3	29	10.3	3	10.3
Vioxx 25	11	501	2.2	6	1.2
Vioxx 50	11	430	2.6	7	1.6
Naproxen	6	406	1.5	1	0.3

* patient-years at risk, provided by sponsor. Additionally, study 068 had 4, 7 and 5 investigator reported serious cv thrombotic events in the VIOXX 25, 50 and naproxen respectively, but only

deaths were referred for adjudication, therefore, events from study 068 are not included in this analysis.

> *Reviewer's comment: Number of events is small. Finding is consistent with VIGOR. There are more CV thrombotic events in rofecoxib groups (12.5, 25 or 50 mg) as compared to naproxen. Interpretation of placebo data is difficult given the small number of patients and short exposure.*

3.2.2 Edema-related AE's in RA application database.

The number of patients with edema-related events was higher in the rofecoxib 25 and 50 mg groups as compared to naproxen.

Table 26. Edema related events* (Source: sponsor's table 13 and 22 RA SUR).

	Placebo n/N %	Rofecox 25 n/N %	Rofecox 50 n/N %	Naproxen n/N %
Placebo controlled phase (12 weeks)	15/989 **1.5**	39/797 **4.9**	23/677 **3.4**	9/516 **1.7**
Long-term continuous (one-year data)	-	36/491 **7.3**	30/458 **6.6**	15/296 **5.1**

* Includes terms such as edema, fluid retention, lower extremity edema, peripheral edema. n= patients with events. N= patients randomized.

3.2.3 Hypertension-related AE's in the RA application database.

Hypertension related events were observed two to three times more often in each of the rofecoxib arms, as compared to the naproxen arm or placebo. A higher percentage of patients presented important increase of blood pressure and required concomitant medication in the rofecoxib arms compared to the naproxen arm. More patients discontinued due to HTN related events from each of the rofecoxib arms as compared to the naproxen arm. Of note, more patients had a prior history of hypertension in the rofecoxib 12.5 mg group.

Table 27. Summary of Hypertension related events in RA application* . (Source Table 13 and 22 RA SUR).

	Placebo n/N %	Rofecox 25 n/N %	Rofecox 50 n/N %	Naproxen n/N %
Placebo controlled phase (12 weeks)	22/989 **2.2**	49/797 **6.1**	43/677 **6.4**	10/516 **1.9**
Long-term continuous (one-year data)	-	59/491 **12.0**	71/458 **15.5**	16/296 **5.4**

* Includes terms such as blood pressure increased, diastolic hypertension, hypertension, uncontrolled hypertension. n= patients with events. N= patients randomized.

Of note, hypertension related events were two to three times more common in the rofecoxib groups as compared to the naproxen group.

3.2.4 CHF related events in RA application database

Three CHF related events occurred during the placebo controlled and long term therapy periods. All in the rofecoxib 50 mg group. Two additional cases occurred in the extension period, one in rofecoxib 25 mg and one in rofecoxib 50 mg. The number of CHF events is small to draw definitive conclusions but is consistent with VIGOR in which rofecoxib 50 mg was associated with higher risk of developing CHF related events than naproxen.

Table 28. Summary of CHF-related events (Source: Tables 13, 22 and 31, RA SUR)

	Placebo n/N	%	Rofe 25 n/N	%	Rofe 50 n/N	%	Naproxen n/N	%
Placebo controlled phase (12 weeks)	0/898	**0**	0/797	**0**	1/677	**0.1**	0/516	**0**
Long-term continuous (one-year)	-		0/491	**0**	2/458	**0.4**	0/296	**0**

* Includes pulmonary edema, congestive heart failure and cardiac failure. n= patients with events. N= patients randomized.

Reviewer's comment: In this database, rofecoxib 25 mg and 50 mg had higher incidence of cardiovascular thrombotic events, HTN-, edema- and CHF-related events compared to naproxen 1000 mg/day or placebo.

B. Additional relevant data

Appendix 1. Narratives of Deaths

Patients allocated to Rofecoxib

065- 5005. Cause of death listed as "Hypertensive heart disease"

73 F, Hx HTN, hyperlipidemia, soft systolic murmur and hyokalemia. Not on ASA. Sept 11, 99 allocated to rofecoxib.

patient called son with c/o SOB When son arrived the patient was dead. Last contact with patient was on Oct 6, 99 when she indicated lack of efficacy. An autopsy was performed. Cause of death as per the coroner was "hypertensive heart disease and that the manner of death was "natural".

In the opinion of FDA reviewers' this is a case of sudden death. **THIS CASE HAD NOT BEEN REFERRED FOR ADJUDICATION TO THE CV ADJUDICATION COMMITTEE**.

200- 3700. Cause of death listed as MI. This case was adjudicated as Sudden Death.

74 M, hx angina, CAD, hyperchol, hypothyr, DM, CABG (1964), GI bleeding. Concom therapy symvastatin, lisinopril, cyclobenzaprine, **ASA**, furosemide, levothyroxine, glyburide. In August 18, 99 allocated to rofecoxib. In patient was thought to have suffered a massive MI. He expired at home. Autopsy not performed.

210- 4856. Cause of death: Glioblastoma multiforme

71 F, allocated to rofecoxib on Sept 29, 99. On Oct 8,99 patient had change in mental status. Oct 21 left side weakness and seizures. CT scan of head, large glioma in the frontal lobe. Patient expired .

658 – 4049. Cause of death listed as MI. Adjudicated as Sudden Death.

71 M, hx Afib, HTN, CAD. Conc; digoxin, diltiazem. No ASA.
Oct 15, 99 allocated to rofecoxib.
Patient attended visti 2 on Nov 22, 99 witout compaints. On family informed the investigator that patient had been found dead in his home.

679- 3423. Cause of death listed as arterial rupture. Autopsy: Ruptured Aortic Aneurism.

75 F, no cv risk factors. Aug 24, 99 allocated to rofecoxib. August 25 reported pruritus and metallic taste. Reported she was under process of diagnostic testing for hematuria. On morning patient was found dead in her kitchen. Autopsy showed ruptured aortic aneurism.

Patients allocated to Naproxen

059-1841 Cause of death malignant neoplasm: gallbladder carcinoma

56F allocated to naproxen Jul 2, 99. Patient reported she has been hospitalized in cholecystectomy and was diagnosed with gallbladder carcinoma. In the patient expired.
702-7154 Cause of death: malignang neoplasm: pancreatic carcinoma.

79F, hx of DM, HTN , anasarca, abdominal pain with constipation. In Oct 27, 99 allocated to naproxen. increasing abdominal pain and distention. CT scan of abdomen showed large pancreatic mass 5.7 cm in the tail of the pancreas w/metastatic disease to the liver. Patient expired .

777-3105 Cause of death: acute renal failure; respiratory failure; acidosis

74 F, hx of HTN, CHF, depression, cellulitis. Baseline labs K 5.4 mEq/L, BUN 49 mg/dl, Creatinine 1.5 g/dL, uric acid 11.4 mg/dL.
Augst 26, 99 patietn allocated to naproxen. Conc Verapamil, lisinopril, furosemide, fluoxetine. admited to ER with respiratory distress, Cxray c/w CHF pneumonia or both. EKG IV conduction delay, sinus rhythm and first degree AV block. Creatinine of 4.8. UA WBC 5-7; RBC 10-12, bacteria 3+, mucus 3+. Patient diagnosied with acute renal failure. Echocardiogram showed enlarged right sided chambers with severe tricuspid regurgitation and pulmonary HTN and calcified mitral valve anulus. Patient deteriorated with elevated WBC count of 19l1 K/L, HB 8.5 mg/dL, severe mixed metabolic and respiratory acidosis. Patient expired in .
Last contact between patient and study coordinator was Oct 21, 99, at the 6 week visit. At that time the patient had a cold and had no complaints. Additional follow up stated that study therapy was dc on Oct 20,99 due to bronchitis.

In summary, this is a patient with history of HTN, CHF, tricuspid regurgitation and pulmonary hypertension and borderline renal function who started naproxen 500 mg bid on August 99. In she presented to the ER with acute renal failure, respiratory failure and acidosis, and died two days later. The investigator considered the episode not related to study medication. The cause of death in this patient is not clear. We might hypothesize that an NSAID worsened her borderline renal function and exacerbated her CHF. However, she may also have been septic. She did have an elevated WBC of 19 K but there are no available blood/urine/sputum cultures.

0831- 7114 Cause of death: Non-small cell carcinoma

78 M, hx glaucoma, doe, COPD peripheral vascular disoerder and smooker. Conc included ASA. Allocated Nov 19 99. Nov 23 99 rx disc due to nabdominal bloating. patient hospitalized and diagnosed with metastatic adenocarcinoma of the lung and died on .

Appendix 2. Serious AE's that resulted in hospitalization

Fifty-three out of 68 (78%) patients with serious AE's in the rofecoxib group and 48 out of 72 (67%) patients with serious AE's in the naproxen group, required hospitalization.

Appendix 2. Hospitalizations (Source: Sponsor's Table 60, appendix 4.1.62)

Rofecoxib 25 mg	Naproxen 1000 mg

Vascular SAE Terms (CRISP Broader Term)
Eligible for Case Adjudication

In the absence of other events identifying adverse experiences (most of which are likely to b serious adverse events), the following events (marked in strikethrough font) will have a low likelihood (in and of themselves) of being thromboembolic events. They may follow thromboembolic events, but alone do not represent such events.

acute myocardial infarction
angina pectoris
anterior spinal artery obstruction
~~aortic atherosclerosis~~
~~aortic disorder~~
aortoiliac obstruction
arterial embolism
arterial occlusion
arterial thrombosis
~~asystole~~
~~atherosclerosis~~
~~atrial fibrillation~~
~~atrial flutter~~
basilar artery obstruction
brachial artery occlusion
~~bundle branch block~~
~~cardiac aneurysm~~
cardiac arrest
cardiac catheter complication
~~cardiac dyskinesia~~
~~cardiac output low~~
cardiac stress test abnormality
cardiac thrombosis
cardiogenic shock
~~cardiomyopathy~~
cardiovascular disorder
cardiovascular hemodynamics abnormality
carotid artery disorder
carotid artery obstruction
cerebellar artery obstruction
cerebellar hemorrhage
cerebral artery obstruction
cerebral atherosclerosis
cerebral hypoxia
cerebral infarction
cerebral ischemia
cerebral thrombosis
cerebrovascular accident
cerebrovascular disorder
~~congestive heart failure~~
~~cor pulmonale~~
coronary artery disease
coronary artery occlusion
coronary artery stenosis
coronary vasospasm
coronary vessel surgery complication
cyanosis
deep venous thrombosis
electrocardiographic abnormality
~~electromechanical dissociation~~
embolic stroke
embolism
endocardial disorder
endocardial thrombus
extracranial artery obstruction
extradural hemorrhage
femoral artery occlusion
gangrene
~~idioventricular rhythm~~
iliac artery occlusion
~~incomplete left bundle branch block~~
intermittent claudication
intracranial hemorrhage
intracranial venous sinus phlebitis
ischemic heart disease
lacunar infarction
~~left bundle branch block~~
lower extremity arterial occlusion
lower extremity ischemia
myocardial infarction
myocardial infarction complication
myocardial reinfarction
myocardial rupture
non-Q-wave myocardial infarction
nonspecific ST-T change
old myocardial infarction

papillary muscle disorder
~~peripheral atherosclerosis~~
peripheral ischemia
peripheral pulse absent
peripheral pulse decreased
peripheral vascular disorder
popliteal artery occlusion
~~pulmonary edema~~
pulmonary embolism
pulmonary infarction
pulmonary thrombosis
pulmonary vascular disease
pulmonary veno-occlusive disease
pulse absent
Q-wave abnormality
Q-wave myocardial infarction
QRS complex abnormality
shock
sinus thrombosis
small vessel disease
ST segment abnormality
ST segment depression
ST segment elevation
ST-T change compatible with ischemia
subclavian steal syndrome
sudden death
superior vena cava thrombosis
T-wave abnormality
T-wave flat
T-wave inversion
thromboembolic stroke
thromboembolism
thrombolysis
thrombophlebitis
thrombophlebitis migrans
thrombosis
thrombotic microangiopathy
transient ischemic attack
ulnar artery occlusion
unstable angina
upper extremity arterial occlusion
upper extremity ischemia
~~varicosity~~
vascular disorder
vascular graft occlusion
vascular insufficiency
vascular occlusion
vasospasm
venous compression
venous disorder
~~venous insufficiency~~
venous occlusion
venous thrombosis
ventricular fibrillation
ventricular flutter
ventricular tachycardia
ventricular thrombus
vertebral artery obstruction
vertebrobasilar insufficiency

(Source: NDA 21-042/s007, Appendix 3.2.1).

Appendix 3.b Sponsor's cardiovascular analyses.

Table Summary analysis of investigator reported serious cardiovascular thrombotic SAE's in ADVANTAGE.

Cohort	Treatment Group	N	Patients with Events	PYR[1]	Rates[2]	Relative Risk[3]	
						Estimate	95% CI
Total cohort	Rofecoxib	2785	14	639	2.19	1.06	(0.50, 2.26)
	Naproxen	2772	13	629	2.07		
Low dose aspirin user	Rofecoxib	352	5	81	6.18	5.08	(0.57, 240.4)
	Naproxen	367	1	82	1.22		

[1]Patient-years at risk

[2]Per 100 PYR

[3]Relative risk of rofecoxib with respect to naproxen from unstratified Cox model where the number of cases is at least 11, otherwise relative risk is ratio of rates.

Source: sponsor's table 80. Appendix 4.1.80

Table. Summary of analysis of adjudicated thrombotic CV SAE in ADVANTAGE

Cohort	Treatment Group	N	Patients with Events	PYR[1]	Rates[2]	Relative Risk[3]	
						Estimate	95% CI
Total cohort	Rofecoxib	2785	9	640	1.41	0.74	(0.31, 1.75)
	Naproxen	2772	12	629	1.91		
Low dose aspirin user	Rofecoxib	352	3	81	3.71	3.05	(0.24, 159.9)
	Naproxen	367	1	82	1.22		

[1]Patient-years at risk

[2]Per 100 PYR

[3]Relative risk of rofecoxib with respect to naproxen from unstratified Cox model where the number of cases is at least 11, otherwise relative risk is ratio of rates.

Source: sponsor's table 78 Appendix 4.1.78

Table Summary of analysis of APTC endpoints in ADVANTAGE

Cohort	Treatment Group	N	Patients with Events	PYR[1]	Rates[2]	Relative Risk[3]	
						Estimate	95% CI
Total cohort	Rofecoxib	2785	10	640	1.56	1.41	(0.54, 3.69)
	Naproxen	2772	7	629	1.11		
Low dose aspirin user	Rofecoxib	352	3	81	3.71	.	.
	Naproxen	367	0	82	0.00		

[1]Patient-years at risk

[2]Per 100 PYR

[3]Relative risk of rofecoxib with respect to naproxen from unstratified Cox model where the number of cases is at least 11, otherwise relative risk is ratio of rates.

Source: sponsor's table 79 Appendix 4.1.79

APTC: Anti Platelet Trialist Collaboration endpoints: CV death, non-fatal MI, non-fatal stroke. (Difference with "Adjudication thrombotic endpoints": Includes hemorrhagic stroke. Excludes angina, TIA and peripheral arterial and venous events).

Appendix 4. Narratives of patients for which FDA reviewers did not agree with sponsor's adjudication.

102 462 1867 - 84 year old woman with history of DM, osteoporosis, hypothyroidism and partial gastrectomy allocated to receive naproxen in July 29 1999. Concomitant therapy included estrogens, insulin and synthroid. On she was hospitalized for severe back pain with a vertebral compression fracture. She was transferred to a rehab center in . In she developed leg edema, was diagnosed with DVT and started anticoagulation. Subsequently developed colon hemorrhage (9/15/99) secondary to anticoagulation. The case report form originally had 8/16/99 as the stop date for taking the study medication. The date was later corrected to 7/9/99. There is a hand written note stating that it is not known whether the patient ever took the assigned medication because she did not return the diary. <u>As per the sponsor's June 22, 2001 correspondence, the event occurred more than 14 days after discontinuation of study drug.</u>

102 065- 5005. 73 year old woman with history of HTN, hyperlipidemia, soft systolic murmur and hyokalemia. Allocated to rofecoxib in Sept 11, 1999. In patient called son with c/o SOB. When son arrived the patient was dead. Last contact with patient at the study site had been in Oct 6, 1999 when she indicated lack of efficacy. An autopsy was performed. Cause of death as per the coroner was "hypertensive heart disease" and that the manner of death was "natural". This is actually a sudden death.

102 0215 4378 211: 72 year old female with history of hyperlipidemia, CVA and carotid endarterectomy. Concomitant meds: ASA, clopidogrel, prevastatin, estradiol. Patient was randomized in Oct 6, 1999. In patient developed numbness and tingling similar to her prior CVA. She went to surgery. A thrombus of the right carotid artery with severe stenosis was found intraoperatively. This case was considered "non-thromboembolic" by the CV adjudication committee. The Division of Neuropharm products considered this case as an "ischemic cerebrovascular accident". This patient was on rofecoxib 25 mg.

102 0386 3155 209: 77 year old female with history of HTN, hyperlipidemia, hypothyroidism, DM and dyspepsia. Concomitant therapy included omeprazole, atenolol, nifedipine, atrovastatin, levothiroxine, clopidogrel temazepam, rosiglitazone, potassium and furosemide. Patient was randomized in June 18, 1999. In Aug 5,1999, a physician reported that the patient developed abnormal head and arm movements diagnosed as dyskinesia of unknown cause. Study therapy was discontinued. Follow up information from a physician indicated that the diagnosis was changed to possible small CVA. In an MRI showed lacunar type infarctions bilaterally in the caudate region; an old hemorrhagic infarct in the right putamen and bilateral thalamic lacuna with no definitive evidence of acute infarct. Patient recovered within 5 days with "adjustment" of medications and haloperidol. This event was adjudicated as "ischemic with small artery occlusion". Acute choreic symptoms can rarely be caused by a lacunar infarct. Acute symptoms are most likely related to metabolic imbalances, e.g. hyperglycemia, which the patient had, exceeding 450 mg/dL during her hospital stay. The Division of Neuropharm products considered this case as "Unable to adjudicate. Acute chorea of unknown etiology". This patient was on naproxen.

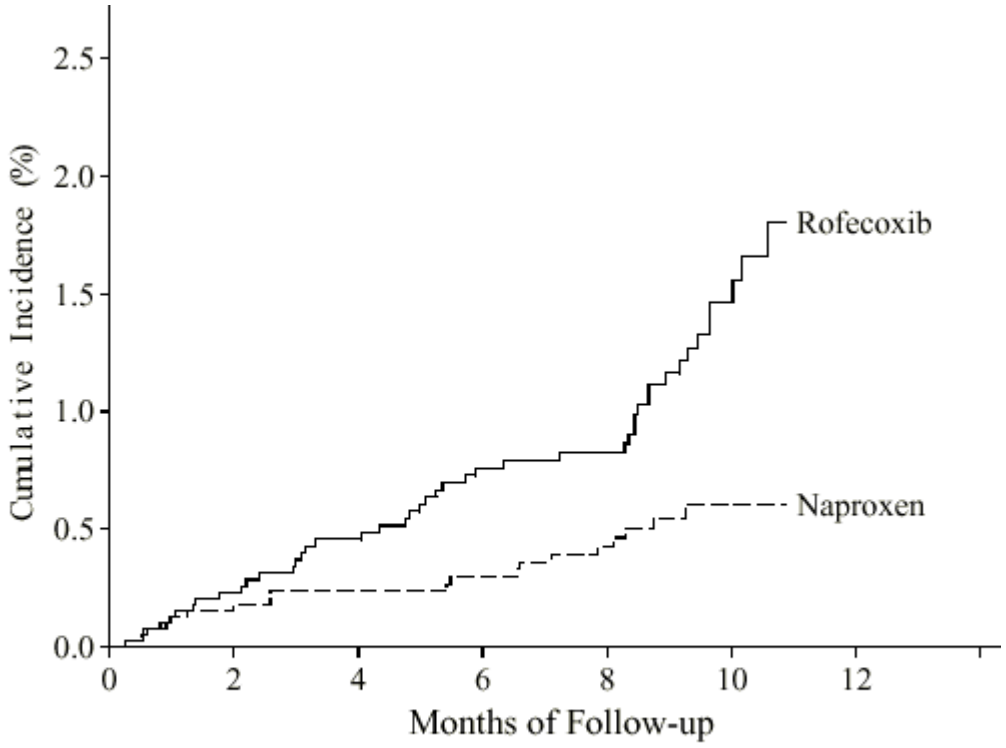
102 0283 2182 222 58 year old female with history of cardiac murmur, allergic cough and intermittent anemia. Patient family history includes development of TIA's with symptoms including dysphagia. Patient was randomized in July 21, 1999. Concomitant medications included conjugated estrogenic hormone w/medroxyprogesterone and famciclovir. Documentation for this case is poor and confusing. In August 5, 1999 for no particular reason, she was started on baby ASA "for general health". Apparently, starting August 16, 1999 the patient had one or two neurologic episodes characterized by speech difficulty and left side weakness in the context of severe headache. In September 11, 1999 ASA was increased from baby ASA to 235 mg/day.

Between September 23, 1999 and October 12, 1999 she had another transient episode of dysphagia for 24 hours. The adjudication package and narrative provided by the sponsor is unclear as to when exactly those TIA's occurred. The patient did not look for medical attention at the time of the events. Additionally, recurrent episodes of weakness appeared to precede study entry. Neurologic examination did not confirm left side weakness. Head CT, carotid ultrasound and echocaridogram (September 24-27) were all normal. The patient completed the trial in October 12, 1999. The CV adjudication committee adjudicated these events as "ischemic CV stroke". The Division of Neuropharm products considered this case to be "Unable to adjudicate". The patient was on naproxen.

903 0002 9009 308. 60 year old male with a history of osteoarthritis, obesity, HTN, and hypercholesterolemia. His PMH is significant for a history of a subendocardial MI in 1990. A coronary angiogram in 1991 revealed 'normal coronary arteries with a bit slow flow'. He had several normal stress tests in the past. He was diagnosed with Syndrome X. The patient was randomized and took study drug for approximately 80 days before the onset of chest pain leading to hospitalization. Chest pain lasted 2.5 hours (6 pm to 8:30 pm), was associated with nausea and not affected by 6 nitroglycerin tablets. ECGs on admissions showed no ischemic changes. Per the hospital discharge summary, MI was excluded *despite an elevated CPK-MB (5 mcg/ml on admission, normals 0 to 3 mcg/ml) and troponin (0.8, normals 0-0.4).* After an echocardiogram and a stress test that was reported as negative ('without steadily ground for ischemia') the patient's pain was attributed to Syndrome X and discharged. The event was adjudicated as not an APTC endpoint per the CV adjudication committee. Because of the persistently elevated CPK-MB and troponin, in the presence of chest pain accompanied by nausea and chest pressure, in patient with prior history of CAD (subendocardial MI) the division of Cardio-Renal products considered this event likely to be due to a cardiac thrombotic event. The patient was on rofecoxib.

Appendix 5. a. Cardiovascular safety in VIGOR study

Confirmed (Adjudicated) Thrombotic CV serious adverse experiences in the VIGOR study. Time to event plot (all patients randomized). RR=2.37 for rofecoxib relative to naproxen (p=0.001).



# at Risk						
Rofecoxib	n=4047	3643	3405	3177	2806	1067 531
Naproxen	n=4029	3647	3395	3172	2798	1073 514

Appendix 5.b. VIGOR study. Confirmed or "adjudicated" thrombotic cardiovascular serious adverse experiences in all patients randomized and in subgroups of patients

identified retrospectively by the sponsor as patients who may have or may have not benefited from low dose ASA.

	N	Patients with events (%)	PYR[1]	Rates[2]	Relative risk[3]		
					Estimate	95%CI	p
All patients randomized							
Rofecoxib	4047	45 (1.1%)	2697	1.67	2.37	1.39 – 4.06	0.0016
Naproxen	4029	19 (0.5%)	2698	0.70			
Potential candidate for low dose ASA[5]							
Rofecoxib	170	15 (8.8%)	105	14.29	4.89	1.41 - 16.88	0.0122
Naproxen	151	3 (2.0 %)	102	2.94			
Not candidate for low dose ASA							
Rofecoxib	3877	30 (0.8%)	2592	1.16	1.88	1.03 – 3.45	0.041
Naproxen	3838	16 (0.4%)	2596	0.62			

[1] Patient-years at risk. [2] Per 100 patients years. [4] Relative risk of rofecoxib with respect to naproxen. [5] Patients with past medical history of cerebrovascular accident, transient ischemic attack, myocardial infarction, unstable angina, stable angina, coronary artery bypass surgery or percutaneous coronary intervention. (Source: modified from sponsor's Table 9 of the safety update, Estimate calculated by Dr. Qian Li, FDA statistician).
VIGOR study. Myocardial Infarctions. Subgroup analyses by sponsor's retrospective identification of patients who may have benefited from low dose ASA.

Appendix 5.c. VIGOR. Investigator reported and adjudicated (CV committee confirmed) serious CV thrombotic events. (Source: NDA 21-042/007, SUR 10/3/01 submission).

	Number of patients with Investigator reported serious CV thrombotic events		Number of patients with CV Committee confirmed serious CV-thrombotic events	
	Rofecoxib (N=)	Naproxen (N=)	Rofecoxib (N=	Naproxen (N=)
	64	**32**	**47**	**20**
CV death	**7**	**7**	**6**	**6**
Fatal acute MI	3	4	2	-
Fatal hemorrhagic stroke	-	-	1	1
Fatal Ischemic stroke	2	1	-	1
Sudden cardiac death	2	-	3	4
Intracranial hemorrhage	-	2	-	-
Cardiac events (fatal & nonfatal)	**36**	**19**	**28**	**10**
MI	23	8	20	4
Angina	6	7	3	4
Vent fib	1	-	5	3
Cardiac arrest	1	-	-	-
Coronary art disease/oclusion	2	3	-	-
Ischemic heart dz.	2	1	-	-
Cerebrovascular (fatal& nonfatal)	**20**	**11**	**13**	**9**
CVA	15	6	-	-
Hemorrhagic stroke	-	-	2	1
Ischemic cerebr.vasc stroke	-	3	9	8
TIA	2	-	2	-
Carotid artery obstruction	1	-	-	-
Cerebrovascular disorder	1	2	-	-
Intracranial hemorrhage	1	2	-	-
Peripheral	**8**	**2**	**6**	**1**
Arterial thrombosis	1	1	1	-
Venous thrombosis	5	1	5	1
Peripheral vascular disorder	1	-	-	-
Arterial embolism	1	-	-	-

Appendix 6. a. Deaths in Alzheimer's protocol # 091

Rofecoxib 25 mg (14)

*AN 332 - Cardiac arrest , fatal MI: 78 M, 1 day off drug, relative day 328
*AN 601 – Sudden death: 75 M, 1 day off drug, relative day 228
*AN 831 – CVA: 85 W M, relative day 296
AN 915 - CHF and pneumonia: 79 F, relative day 260
AN 964 - Dizziness, CVA, respiratory failure: 86 F, taking conjugated estrogens, developed CVA approx. 1 month into the study. Drug stopped. Patient died on relative day 58. Not adjudicated due to insufficient data.
AN 3 - Pneumonia: 91 F day 260
AN 42 - Endocarditis/pneumonia: 83 M, day 303
AN 282 – Lung cancer: 71 F, day 165
AN 376 - Burn/fungemia/anuria: 62 M, day 173
AN 382 - Lung and brain malignant neoplasm: 77 F, relative day 123
AN 542 - Hypercalcemia, acute renal failure: 82 F 7 days off drug; relative day 188
AN 691 - Esophageal malignant neoplasm: 86 M, relative day onset 390
AN 835 - Interstitial lung disease, pneumonia, cardiac arrest: 82 M, day 269
AN 891 - Fever, sepsis. 88 F, day 76

Placebo (8)

*AN 784 – Sudden death: 70 F, day 458
AN 394 - Metastatic neoplasm, unknown primary: 68 M, day 452
AN 613 - COPD/ aspiration pneumonia: 88 M, day 131
AN 664 - Alzheimer's/Pneumonia: 84 M, day 417
AN 827 - Intracranial hemorrhage: 74 M, day 70 (CV non-thromboembolic)
AN 830 - Acute myelogenous leukemia: 79 F, day 99
AN 832 - Pneumonia, cardiac arrest secondary to aspiration/sepsis: 82 M, day 461
AN 956 - Ruptured aortic aneurysm: 81 M, day 16 (CV non-thromboembolic)

* Case confirmed by Cardiovascular Adjudication Committee

Appendix 6b. Deaths in Alzheimer's protocol # 078 (from WAES database)

Rofecoxib 25 mg (15)

*AN 248 – Sudden death, unknown cause of death: 71 F, day 747
*AN 359 - Sudden death, hypertension: 68 M, day 624
*AN 737 - Sudden death, cardiac arrest: 84 M, day 185
*AN 799 - Sudden death, cardiac arrest: 85 M, day 312
*AN1025 – Acute Myocardial infarction: 83 M, day 138
AN 205 - Postop complication, hip fracture, pulmonary embolism: 85 M, day 496 (CV)
AN 583 - Pulmonary embolism/ pancreatic ca: 70 M, day 357 (CV)
AN 352 - Hemorragic duodenal ulcer; small cell ca; 67 M, day 322
AN 762 - Metastatic prostate ca, renal failure; 87 M, day 707
AN 821 - Head trauma: 85 M, day 271
AN 935 - Trauma: 75 M, day 106
AN 1097 – Electric shock: 69 M , day 248
AN 1453 – Chest trauma: 83 M, day 611
AN1453 – Bacterial sepsis, acute myelogenous leukemia: 80 M, day 53

Placebo (8):

*AN 1256 – Sudden death: 82 F, day 674
*AN 1378 – Sudden death: 74 M, day 392
AN 539 - Hypertension: 72 M, day 243 (CV).
AN 264 – Colon ca: 76 M, day 430
AN 294 - malignant melanoma: 77 M, day 556
AN 308 - myelogenous lukemia, pneumonia, acute renal failure: 85 M, day 407
AN 1144 - Pancreatic carcinoma: 94 F, day 469
AN 1350 - bladder carcinoma: 79 F, day 708
AN 1547 - metastatic neoplasm of unknown origin: 82 M, day 96

Deaths in Alzheimer's protocol #126

Rofecoxib (4)

AN 125 - GI (large intestine) perforation: 86 F, day 214
AN 466 - Hip fracture, dyspnea (PE?): 86 M, day 190 NOT REFERRED x adjudication
AN 532 - Hemorragic CVA (confirmed)
AN 743 - Intracranial hemorrhage (confirmed)

Placebo (3)

*AN 661 - Myocardial infarction, related to major stressor: meningitis: 77 M, day 236
AN 257 - Trauma: 79 M, day 82
AM 635 - Lymphoma, GI bleeding, sepsis: 78 F, day 216

* Confirmed as cardiovascular thrombotic event by CV Adjudication Committee. Of note, mean exposure in this study was 5 months only.